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(54) Title: 2-AMINO-2-ALKYL-3 HEPTENOIC AND HEPTYNOIC ACID DERIVATIVES USEFUL AS NITRIC OXIDE SYNTHASE INHIBITORS

(57) Abstract: The present invention relates to 2-amino-2-alkyl-3 heptenoic and heptynoic as derivatives and their use in therapy, in particular their use as nitric oxide synthase inhibitors.

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2-Amino-2-Alkyl-3 Heptenoic and Heptynoic Acid Derivatives
Useful as Nitric Oxide Synthase Inhibitors

Cross Reference to Related Applications

- 5 This application claims the benefit of U.S. Provisional Application Serial No. 60/232,684, filed September 15, 2000.

Field of the Invention

- 10 The present invention relates to 2-amino-2-alkyl-3 heptenoic and heptynoic acid derivatives and their use in therapy, in particular their use as nitric oxide synthase inhibitors.

Related Art

- 15 It has been known since the early 1980's that the vascular relaxation caused by acetylcholine is dependent on the vascular endothelium. The endothelium-derived relaxing factor (EDRF), now known to be nitric oxide (NO) is generated in the vascular endothelium by nitric oxide synthase (NOS). The activity of NO as a vasodilator has been known for well over 100 years. In addition, NO is the active species deriving from amyl nitrite, glyceryl trinitrate and other nitrovasodilators. The identification of EDRF as NO has coincided with the discovery of a biochemical
20 pathway by which NO is synthesized from the amino acid L-arginine by the enzyme NO synthase.

- Nitric oxide is an endogenous stimulator of the soluble guanylate cyclase. In addition to endothelium-dependent relaxation, NO is involved in a number of biological actions including cytotoxicity of phagocytic cells and cell-to-cell
25 communication in the central nervous system.

 There are at least three types of NO synthase as follows:

- (i) a constitutive, Ca^{++} /calmodulin dependent enzyme, located in the endothelium, that releases NO in response to receptor or physical stimulation.
- (ii) a constitutive, Ca^{++} /calmodulin dependent enzyme, located in the brain,
30 that releases NO in response to receptor or physical stimulation.

(iii) a Ca^{++} independent enzyme which is induced after activation of vascular smooth muscle, macrophages, endothelial cells, and a number of other cells by endotoxin and cytokines. Once expressed, this inducible nitric oxide synthase (hereinafter "iNOS") generates NO continuously for long periods.

5 The NO released by each of the two constitutive enzymes acts as a transduction mechanism underlying several physiological responses. The NO produced by the inducible enzyme is a cytotoxic molecule for tumor cells and invading microorganisms. It also appears that adverse effects of excess NO production, in particular pathological vasodilation and tissue damage, may result
10 largely from the NO synthesized by iNOS.

 There is a growing body of evidence that NO may be involved in the degeneration of cartilage which takes place as a result of certain conditions such as arthritis and it is also known that NO synthesis is increased in rheumatoid arthritis and in osteoarthritis.

15 Some of the NO synthase inhibitors proposed for therapeutic use are non-selective; they inhibit both the constitutive and the inducible NO synthases. Use of such a non-selective NO synthase inhibitor requires that great care be taken in order to avoid the potentially serious consequences of over-inhibition of the constitutive NO-synthase, such consequences including hypertension and possible thrombosis
20 and tissue damage. In particular, in the case of the therapeutic use of L-NMMA (a non-selective NO synthase inhibitor) for the treatment of toxic shock it has been recommended that the patient must be subject to continuous blood pressure monitoring throughout the treatment. Thus, while non-selective NO synthase inhibitors have therapeutic utility provided that appropriate precautions are taken,
25 NO synthase inhibitors which are selective in the sense that they inhibit the inducible NO synthase to a considerably greater extent than the constitutive isoforms of NO synthase would be of even greater therapeutic benefit and easier to use (S. Moncada and E. Higgs, FASEB J., 9, 1319-1330, 1995).

 PCT International Publication No. WO 93/13055 and U. S. Patent No.
30 5,132,453, the disclosure of which are hereby incorporated by reference in their

entirety as if written herein, disclose compounds that inhibit nitric oxide synthesis and preferentially inhibit the inducible isoform of nitric oxide synthase.

PCT International Publication No. WO 95/25717 discloses certain amidino derivatives as being useful in inhibiting inducible nitric oxide synthase.

5 Various attempts have been made to improve the potency and selectivity of NOS inhibitors by adding one or more rigidifying elements to the inhibitor's structure. Publications by Y. Lee et al (Bioorg. Med. Chem. 7, 1097 (1999)) and R. J. Young et al (Bioorg. Med. Chem. Lett. 10, 597 (2000)) teach that imposing conformational rigidity with one or more carbon-carbon double bonds is not a
10 favorable approach to impart selectivity for NOS inhibitors.

Summary of the Invention

Compounds have now been found which have the advantage of being very efficacious in the human cartilage explant assay, a model for osteoarthritis.

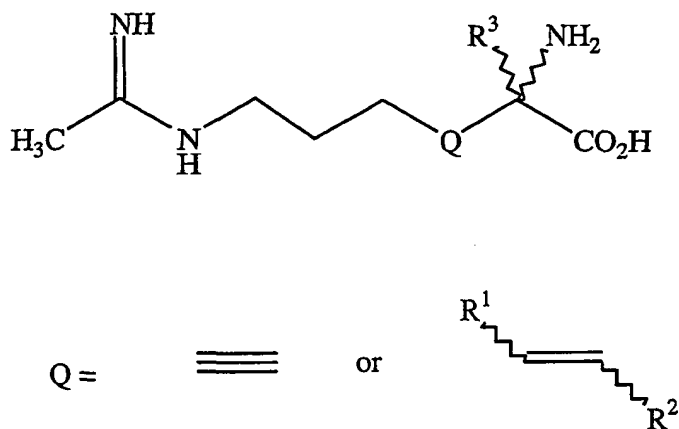
The present disclosure teaches that a carbon-carbon double bond can be used
15 as a rigidifying element, and the resulting compounds will have unexpected potency and selectivity for inhibition of inducible NOS.

Moreover, the publication by Y. Lee et al (Bioorg. Med. Chem. 7, 1097 (1999)) teaches that when a carbon-carbon double bond is used to constrain the arginine backbone, the geometric isomer placing the carbon framework in a cis or Z
20 orientation produces a less favorable interaction with NOS. In contrast, olefinic derivatives of arginine placing the carbon framework in the trans or E configuration are better substrates. The present disclosure teaches that a carbon-carbon double bond imparts a favorable interaction with inducible NOS, such that the resulting compounds have unexpected potency and selectivity for inhibition of inducible
25 NOS over the constitutive isoforms.

Further, compounds of the present invention have the advantage of being very efficacious as iNOS inhibitors in the human cartilage explant assay, a model for osteoarthritis. At the same time the compounds of the present invention are surprisingly less able to penetrate certain non-target organs in test systems,
30 especially in comparison to the compounds of WO 93/13055. This surprising

differentiation in expected access between the target organ (cartilage) and other organs is an unexpected advantage for the compounds of the present invention.

In a broad aspect, compounds of the present invention are represented by:



5

or a pharmaceutically acceptable salt thereof, wherein:

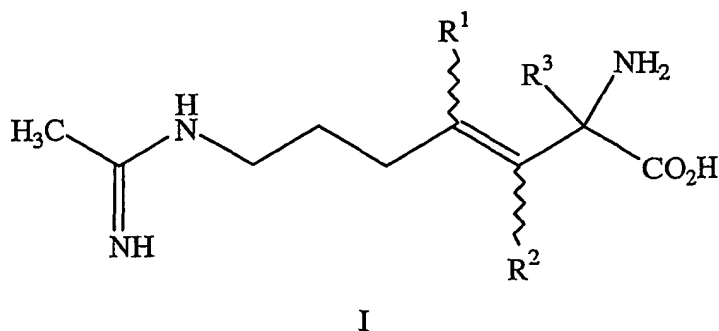
R¹ is selected from the group consisting of hydrogen, halo, C₁-C₅ alkyl and C₁-C₅ alkyl substituted by alkoxy or one or more halo;

10 R² is selected from the group consisting of hydrogen, halo, C₁-C₅ alkyl and C₁-C₅ alkyl substituted by alkoxy or one or more halo;

R³ is C₁-C₅ alkyl or C₁-C₅ alkyl be substituted by alkoxy or one or more halo.

In an embodiment represented by Formula I, the invention relates to:

15



or a pharmaceutically acceptable salt thereof, wherein:

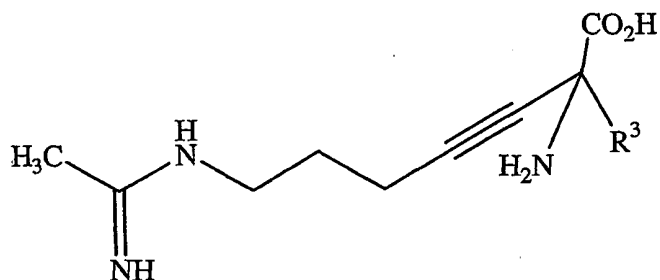
or a pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from the group consisting of hydrogen, halo, C_1 - C_5 alkyl and C_1 - C_5 alkyl substituted by alkoxy or one or more halo;

R^2 is selected from the group consisting of hydrogen, halo, C_1 - C_5 alkyl and C_1 - C_5 alkyl substituted by alkoxy or one or more halo;

5 R^3 is C_1 - C_5 alkyl or C_1 - C_5 alkyl be substituted by alkoxy or one or more halo.

In an embodiment represented by Formula II, the invention relates to:



10

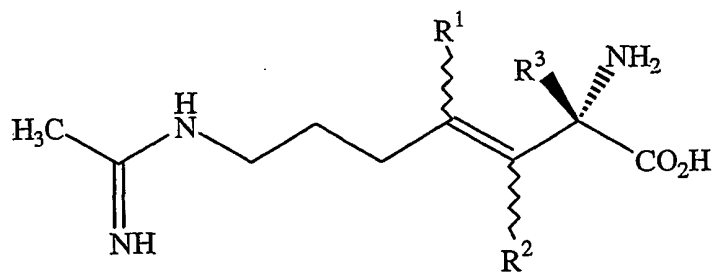
II

or a pharmaceutically acceptable salt thereof, wherein:

R^3 is C_1 - C_5 alkyl, said C_1 - C_5 alkyl optionally substituted by halo or alkoxy, said alkoxy optionally substituted by one or more halo.

In an embodiment represented by Formula III, the invention relates to:

15



III

20 or a pharmaceutically acceptable salt thereof, wherein:

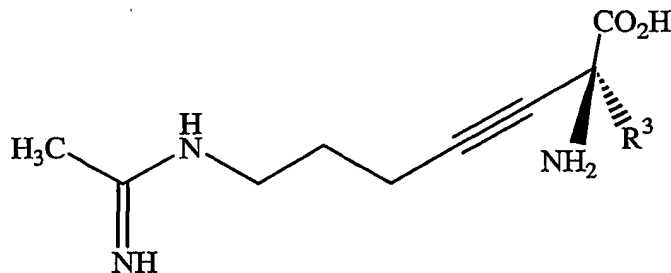
R^1 is selected from the group consisting of hydrogen, halo, C_1 - C_5 alkyl and C_1 - C_5 alkyl substituted by alkoxy or one or more halo;

R^2 is selected from the group consisting of hydrogen, halo, C_1 - C_5 alkyl and C_1 - C_5 alkyl substituted by alkoxy or one or more halo;

R^3 is C_1 - C_5 alkyl or C_1 - C_5 alkyl be substituted by alkoxy or one or more halo.

In an embodiment represented by Formula IV, the invention relates to:

5

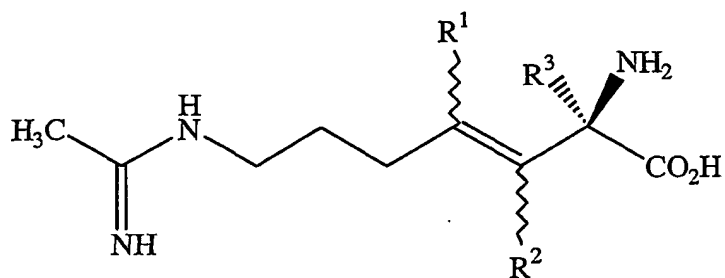


IV

or a pharmaceutically acceptable salt thereof, wherein:

- 10 R^3 is C_1 - C_5 alkyl, said C_1 - C_5 alkyl optionally substituted by halo or alkoxy, said alkoxy optionally substituted by one or more halo.

In an embodiment represented by Formula V, the invention relates to:



15

V

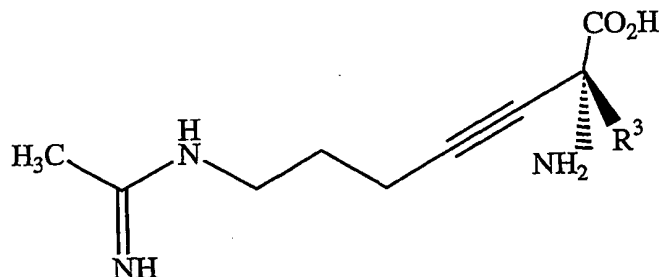
or a pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from the group consisting of hydrogen, halo, C_1 - C_5 alkyl and C_1 - C_5 alkyl substituted by alkoxy or one or more halo;

- 20 R^2 is selected from the group consisting of hydrogen, halo, C_1 - C_5 alkyl and C_1 - C_5 alkyl substituted by alkoxy or one or more halo;

R^3 is C_1 - C_5 alkyl or C_1 - C_5 alkyl be substituted by alkoxy or one or more halo.

In an embodiment represented by Formula VI, the invention relates to:



5

VI

or a pharmaceutically acceptable salt thereof, wherein:

R³ is C₁-C₅ alkyl, said C₁-C₅ alkyl optionally substituted by halo or alkoxy, said alkoxy optionally substituted by one or more halo.

In a broad aspect, the present invention is directed to novel compounds,
10 pharmaceutical compositions, process for preparing novel compounds, process for preparing pharmaceutical compositions, and methods of using said compounds and compositions for inhibiting or modulating nitric oxide synthesis in a subject in need of such inhibition or modulation by administering a compound which preferentially inhibits or modulates the inducible isoform of nitric oxide synthase over the
15 constitutive isoforms of nitric oxide synthase. It is also another object of the present invention to lower nitric oxide levels in a subject in need of such lowering. The present compounds possess useful nitric oxide synthase inhibiting activity, and are expected to be useful in the treatment or prophylaxis of a disease or condition in which the synthesis or over-synthesis of nitric oxide forms a contributory part.

20 Compounds of the present invention will be useful for treating, among other things, inflammation in a subject, or for treating other nitric oxide synthase-mediated disorders, such as, as an analgesic in the treatment of pain and headaches. The compounds of the present invention will be useful in the treatment of pain including somatogenic (either nociceptive or neuropathic), both acute and chronic,
25 and could be used in a situation including neuropathic pain for which a common

NSAID, opioid analgesic or certain anti-convulsants would traditionally be administered.

Included within the scope of the present invention are novel intermediates useful for synthesizing compounds of the present invention.

5 Conditions in which the compounds of the present invention will provide an advantage in inhibiting NO production from L-arginine include arthritic conditions. For example, compounds of the present invention will be useful to treat arthritis, including but not limited to rheumatoid arthritis, spondyloarthropathies, gouty arthritis, osteoarthritis, systemic lupus erythematosus, juvenile arthritis, acute
10 rheumatic arthritis, enteropathic arthritis, neuropathic arthritis, psoriatic arthritis, and pyogenic arthritis.

 Compounds of the invention will be further useful in the treatment of asthma, bronchitis, menstrual cramps (e.g., dysmenorrhea), premature labor, tendinitis, bursitis, skin-related conditions such as psoriasis, eczema, burns,
15 sunburn, dermatitis, pancreatitis, hepatitis, and post-operative inflammation including inflammation from ophthalmic surgery such as cataract surgery and refractive surgery. Compounds of the invention also would be useful to treat gastrointestinal conditions such as inflammatory bowel disease, Crohn's disease, gastritis, irritable bowel syndrome and ulcerative colitis.

20 Compounds of the invention would be useful in treating inflammation and tissue damage in such diseases as vascular diseases, migraine headaches, periarteritis nodosa, thyroiditis, aplastic anemia, Hodgkin's disease, scleroderma, rheumatic fever, type I diabetes, neuromuscular junction disease including myasthenia gravis, white matter disease including multiple sclerosis;
25 sarcoidosis, nephrotic syndrome, Behcet's syndrome, polymyositis, gingivitis, nephritis, hypersensitivity, swelling occurring after injury, myocardial ischemia, and the like.

 The compounds would also be useful in the treatment of ophthalmic diseases, such as glaucoma, retinitis, retinopathies, uveitis, ocular
30 photophobia, and of inflammation and pain associated with acute injury to the

eye tissue. Of particular interest among the uses of the present inventive compounds is the treatment of glaucoma, especially where symptoms of glaucoma are caused by the production of nitric oxide, such as in nitric oxide-mediated nerve damage. The compounds would also be useful in the treatment of pulmonary inflammation, such as that associated with viral infections and cystic fibrosis. The compounds would also be useful for the treatment of certain central nervous system disorders, such as cortical dementias including Alzheimer's disease, and central nervous system damage resulting from stroke, ischemia and trauma. These compounds would also be useful in the treatment of allergic rhinitis, respiratory distress syndrome, endotoxin shock syndrome, and atherosclerosis. The compounds would also be useful in the treatment of pain, including but not limited to postoperative pain, dental pain, muscular pain, pain caused by temporomandibular joint syndrome, and pain resulting from cancer. The compounds would be useful for the prevention of dementias, such as Alzheimer's disease.

Besides being useful for human treatment, these compounds are also useful for veterinary treatment of companion animals, exotic animals and farm animals, including mammals and other vertebrates. More preferred animals include horses, dogs, and cats.

The present compounds may also be used in co-therapies, partially or completely, in place of other conventional antiinflammatory therapies, such as together with steroids, NSAIDs, COX-2 selective inhibitors, matrix metalloproteinase inhibitors, 5-lipoxygenase inhibitors, LTB₄ antagonists and LTA₄ hydrolase inhibitors.

Other conditions in which the compounds of the present invention will provide an advantage in inhibiting NO inhibition include cardiovascular ischemia, diabetes (type I or type II), congestive heart failure, myocarditis, atherosclerosis, migraine, glaucoma, aortic aneurysm, reflux esophagitis, diarrhea, irritable bowel syndrome, cystic fibrosis, emphysema, asthma, bronchiectasis, hyperalgesia (allodynia), cerebral ischemia (both focal ischemia, thrombotic stroke and global

ischemia (for example, secondary to cardiac arrest), multiple sclerosis and other central nervous system disorders mediated by NO, for example Parkinson's disease. Further neurodegenerative disorders in which NO inhibition may be useful include nerve degeneration or nerve necrosis in disorders such as hypoxia, hypoglycemia, 5 epilepsy, and in cases of central nervous system (CNS) trauma (such as spinal cord and head injury), hyperbaric oxygen convulsions and toxicity, dementia, such as, for example pre-senile dementia, and AIDS-related dementia, cachexia, Sydenham's chorea, Huntington's disease, Amyotrophic Lateral Sclerosis, Korsakoff's disease, imbecility relating to a cerebral vessel disorder, sleeping disorders, schizophrenia, 10 depression, depression or other symptoms associated with Premenstrual Syndrome (PMS), anxiety and septic shock.

Still other disorders or conditions which will be advantageously treated by the compounds of the present invention include treatment of prevention of opiate tolerance in patients needing protracted opiate analgesics, and benzodiazepine 15 tolerance in patients taking benzodiazepines, and other addictive behavior, for example, nicotine addiction, alcoholism, and eating disorders. The compounds and methods of the present invention will also be useful in the treatment or prevention of drug withdrawal symptoms, for example treatment or prevention of symptoms of withdrawal from opiate, alcohol, or tobacco addiction. The present inventive 20 compounds may also be useful to prevent tissue damage when therapeutically combined with antibacterial or antiviral agents.

The compounds of the present invention will also be useful in inhibiting NO production from L-arginine including systemic hypotension associated with septic and/or toxic hemorrhagic shock induced by a wide variety of agents; therapy with 25 cytokines such as TNF, IL-1 and IL-2; and as an adjuvant to short term immunosuppression in transplant therapy.

Compounds of the invention are useful for the prevention or treatment of cancer, such as colorectal cancer, and cancer of the breast, lung, prostate, bladder, cervix and skin. The present invention is further directed to the use of 30 the compounds of the present invention for the treatment and prevention of

neoplasias. The neoplasias that will be treatable or preventable by the compounds and methods of the present invention include brain cancer, bone cancer, a leukemia, such as, for example chronic lymphocytic leukemia, a lymphoma, epithelial cell-derived neoplasia (epithelial carcinoma) such as
5 basal cell carcinoma, adenocarcinoma, gastrointestinal cancer such as lip cancer, mouth cancer, esophageal cancer, small bowel cancer and stomach cancer, colon cancer, liver cancer, bladder cancer, pancreas cancer, urogenital cancers, such as ovary cancer, cervical cancer, vulvar cancer, and lung cancer, breast cancer and skin cancer, such as squamous cell, melanoma, and basal
10 cell cancers, prostate cancer, renal cell carcinoma, and other known cancers that effect epithelial cells throughout the body. Compounds of the present invention will be effective as well for treatment of mesenchymal derived neoplasias. Preferably, the neoplasia to be treated is selected from gastrointestinal cancer, liver cancer, bladder cancer, pancreas cancer, ovary
15 cancer, prostate cancer, cervical cancer, vulvar cancer, lung cancer, breast cancer and skin cancer, such as squamous cell and basal cell cancers. The present compounds and methods can also be used to treat the fibrosis which occurs with radiation therapy. The present compounds and methods can be used to treat subjects having adenomatous polyps, including those with
20 familial adenomatous polyposis (FAP). Additionally, the present compounds and methods can be used to prevent polyps from forming in patients at risk of FAP.

Conjunctive treatment of a compound of the present invention with another antineoplastic agent will produce a synergistic effect or alternatively reduce the
25 toxic side effects associated with chemotherapy by reducing the therapeutic dose of the side effect-causing agent needed for therapeutic efficacy or by directly reducing symptoms of toxic side effects caused by the side effect-causing agent. A compound of the present invention will further be useful as an adjunct to radiation therapy to reduce side effects or enhance efficacy. In the present invention, another
30 agent which can be combined therapeutically with a compound of the present

invention includes any therapeutic agent which is capable of inhibiting the enzyme cyclooxygenase-2 ("COX-2"). Preferably such COX-2 inhibiting agents inhibit COX-2 selectively relative to the enzyme cyclooxygenase-1 ("COX-1"). Such a COX-2 inhibitor is known as a "COX-2 selective inhibitor". More preferably, a
5 compound of the present invention can be therapeutically combined with a COX-2 selective inhibitor wherein the COX-2 selective inhibitor selectively inhibits COX-2 at a ratio of at least 10:1 relative to inhibition of COX-1, more preferably at least 30:1, and still more preferably at least 50:1 in an *in vitro* test. COX-2 selective inhibitors useful in therapeutic combination with the compounds of the present
10 invention include celecoxib, valdecoxib, deracoxib, etoricoxib, rofecoxib, ABT-963 (2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methyl-1-butoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone; described in PCT Patent Application No. WO 00/24719), or meloxicam. A compound of the present invention can also be advantageously used in therapeutic combination with a prodrug of a COX-2
15 selective inhibitor, for example parecoxib.

Another chemotherapeutic agent which will be useful in combination with a compound of the present invention can be selected, for example, from the following non-comprehensive and non-limiting list:

Alpha-difluoromethylornithine (DFMO), 5-FU-fibrinogen, acanthifolic acid,
20 aminothiadiazole, brequinar sodium, carmofur, Ciba-Geigy CGP-30694, cyclopentyl cytosine, cytarabine phosphate stearate, cytarabine conjugates, Lilly DATHF, Merrel Dow DDFC, dezaguanine, dideoxycytidine, dideoxyguanosine, didox, Yoshitomi DMDC, doxifluridine, Wellcome EHNA, Merck & Co. EX-015, fazarabine, floxuridine, fludarabine phosphate, 5-fluorouracil, N-(2'-furanidyl)-5-
25 fluorouracil, Daiichi Seiyaku FO-152, isopropyl pyrrolizine, Lilly LY-188011, Lilly LY-264618, methobenzaprim, methotrexate, Wellcome MZPES, norspermidine, NCI NSC-127716, NCI NSC-264880, NCI NSC-39661, NCI NSC-612567, Warner-Lambert PALA, pentostatin, piritrexim, plicamycin, Asahi Chemical PL-AC, Takeda TAC-788, thioguanine, tiazofurin, Erbamont TIF, trimetrexate, tyrosine
30 kinase inhibitors, tyrosine protein kinase inhibitors, Taiho UFT, uricytin, Shionogi

- 254-S, aldo-phosphamide analogues, altretamine, anaxirone, Boehringer Mannheim BBR-2207, bestrabucil, budotitane, Wakunaga CA-102, carboplatin, carmustine, Chinoin-139, Chinoin-153, chlorambucil, cisplatin, cyclophosphamide, American Cyanamid CL-286558, Sanofi CY-233, cyplatate, Degussa D-19-384, Sumimoto
- 5 DACHP(Myrr)2, diphenylspiromustine, diplatinum cytostatic, Erba distamycin derivatives, Chugai DWA-2114R, ITI E09, elmustine, Erbamont FCE-24517, estramustine phosphate sodium, fotemustine, Unimed G-6-M, Chinoin GYKI-17230, hepsul-fam, ifosfamide, iproplatin, lomustine, mafosfamide, mitolactol, Nippon Kayaku NK-121, NCI NSC-264395, NCI NSC-342215, oxaliplatin, Upjohn
- 10 PCNU, prednimustine, Proter PTT-119, ranimustine, semustine, SmithKline SK&F-101772, Yakult Honsha SN-22, spiromustine, Tanabe Seiyaku TA-077, taumustine, temozolomide, teroxirone, tetraplatin, trimelamol, Taiho 4181-A, aclarubicin, actinomycin D, actinoplanone, Erbamont ADR-456, aeroplysinin derivative, Ajinomoto AN-201-II, Ajinomoto AN-3, Nippon Soda anisomycins,
- 15 anthracycline, azino-mycin-A, bisucaberin, Bristol-Myers BL-6859, Bristol-Myers BMY-25067, Bristol-Myers BMY-25551, Bristol-Myers BMY-26605, Bristol-Myers BMY-27557, Bristol-Myers BMY-28438, bleomycin sulfate, bryostatin-1, Taiho C-1027, calicheomycin, chromoximycin, dactinomycin, daunorubicin, Kyowa Hakko DC-102, Kyowa Hakko DC-79, Kyowa Hakko DC-88A, Kyowa Hakko
- 20 DC89-A1, Kyowa Hakko DC92-B, ditrisarubicin B, Shionogi DOB-41, doxorubicin, doxorubicin-fibrinogen, elsamicin-A, epirubicin, erbstatin, esorubicin, esperamicin-A1, esperamicin-Alb, Erbamont FCE-21954, Fujisawa FK-973, fostriecin, Fujisawa FR-900482, glidobactin, gregatin-A, grincamycin, herbimycin, idarubicin, illudins, kazusamycin, kesarirhodins, Kyowa Hakko KM-5539, Kirin
- 25 Brewery KRN-8602, Kyowa Hakko KT-5432, Kyowa Hakko KT-5594, Kyowa Hakko KT-6149, American Cyanamid LL-D49194, Meiji Seika ME 2303, menogaril, mitomycin, mitoxantrone, SmithKline M-TAG, neoactin, Nippon Kayaku NK-313, Nippon Kayaku NKT-01, SRI International NSC-357704, oxalysine, oxaunomycin, peplomycin, pilatin, pirarubicin, porothramycin,
- 30 pyrindamycin A, Tobishi RA-I, rapamycin, rhizoxin, rodorubicin, sibanomicin,

siwenmycin, Sumitomo SM-5887, Snow Brand SN-706, Snow Brand SN-07, sorangicin-A, sparsomycin, SS Pharmaceutical SS-21020, SS Pharmaceutical SS-7313B, SS Pharmaceutical SS-9816B, steffimycin B, Taiho 4181-2, talisomycin, Takeda TAN-868A, terpentecin, thiazine, tricrozarin A, Upjohn U-73975, Kyowa

5 Hakko UCN-10028A, Fujisawa WF-3405, Yoshitomi Y-25024 zorubicin, alpha-carotene, alpha-difluoromethyl-arginine, acitretin, Biotec AD-5, Kyorin AHC-52, alstonine, amonafide, amphethinile, amsacrine, Angiostat, ankinomycin, antineoplaston A10, antineoplaston A2, antineoplaston A3, antineoplaston A5, antineoplaston AS2-1, Henkel APD, aphidicolin glycinate, asparaginase, Avarol,

10 baccharin, batracylin, benfluron, benzotript, Ipsen-Beaufour BIM-23015, bisantrene, Bristo-Myers BMY-40481, Vestar boron-10, bromofosfamide, Wellcome BW-502, Wellcome BW-773, caracemide, carmethizole hydrochloride, Ajinomoto CDAF, chlorsulfaquinoxalone, Chemex CHX-2053, Chemex CHX-100, Warner-Lambert CI-921, Warner-Lambert CI-937, Warner-Lambert CI-941,

15 Warner-Lambert CI-958, clanfenur, claviridenone, ICN compound 1259, ICN compound 4711, Contracan, Yakult Honsha CPT-11, crisnatol, curaderm, cytochalasin B, cytarabine, cytocytin, Merz D-609, DABIS maleate, dacarbazine, datelliptinium, didemnin-B, dihaematoporphyrin ether, dihydrolenperone, dinaline, distamycin, Toyo Pharmar DM-341, Toyo Pharmar DM-75, Daiichi Seiyaku DN-

20 9693, elliprabine, elliptinium acetate, Tsumura EPMTTC, ergotamine, etoposide, etretinate, fenretinide, Fujisawa FR-57704, gallium nitrate, genkwadaphnin, Chugai GLA-43, Glaxo GR-63178, grifolan NMF-5N, hexadecylphosphocholine, Green Cross HO-221, homoharringtonine, hydroxyurea, BTG ICRF-187, ilmofofosine, isoglutamine, isotretinoin, Otsuka JI-36, Ramot K-477, Otsuak K-76COONa,

25 Kureha Chemical K-AM, MECT Corp KI-8110, American Cyanamid L-623, leukoregulin, lonidamine, Lundbeck LU-23-112, Lilly LY-186641, NCI (US) MAP, marycin, Merrel Dow MDL-27048, Medco MEDR-340, merbarone, merocyanine derivatives, methylanilinoacridine, Molecular Genetics MGI-136, minactivin, mitonafide, mitoquidone, mopidamol, motretinide, Zenyaku Kogyo

30 MST-16, N-(retinoyl)amino acids, Nisshin Flour Milling N-021, N-acylated-

dehydroalanines, nafazatrom, Taisho NCU-190, nocodazole derivative, Normosang, NCI NSC-145813, NCI NSC-361456, NCI NSC-604782, NCI NSC-95580, octreotide, Ono ONO-112, oquizanocine, Akzo Org-10172, pancratistatin, pazelliptine, Warner-Lambert PD-111707, Warner-Lambert PD-115934, Warner-Lambert PD-131141, Pierre Fabre PE-1001, ICRT peptide D, piroxantrone, 5 polyhaematoporphyrin, polypreic acid, Efamol porphyrin, probimane, procarbazine, proglumide, Invitron protease nexin I, Tobishi RA-700, razoxane, Sapporo Breweries RBS, restrictin-P, retelliptine, retinoic acid, Rhone-Poulenc RP-49532, Rhone-Poulenc RP-56976, SmithKline SK&F-104864, Sumitomo SM-108, Kuraray 10 SMANCS, SeaPharm SP-10094, spatol, spirocyclopropane derivatives, spirogermanium, Unimed, SS Pharmaceutical SS-554, strypoldinone, Stypoldione, Suntory SUN 0237, Suntory SUN 2071, superoxide dismutase, Toyama T-506, Toyama T-680, taxol, Teijin TEI-0303, teniposide, thaliblastine, Eastman Kodak TJB-29, tocotrienol, Topostin, Teijin TT-82, Kyowa Hakko UCN-01, Kyowa 15 Hakko UCN-1028, ukrain, Eastman Kodak USB-006, vinblastine sulfate, vincristine, vindesine, vinestramide, vinorelbine, vintriptol, vinzolidine, withanolides, Yamanouchi YM-534, uroguanylin, combretastatin, dolastatin, idarubicin, epirubicin, estramustine, cyclophosphamide, 9-amino-2-(S)-camptothecin, topotecan, irinotecan (Camptosar), exemestane, decapeptyl 20 (tryptorelin), or an omega-3 fatty acid.

Examples of radioprotective agents which may be used in a combination therapy with the compounds of this invention include AD-5, adchnon, amifostine analogues, detox, dimesna, I-102, MM-159, N-acylated-dehydroalanines, TGF-Genentech, tiprotimod, amifostine, WR-151327, FUT-187, ketoprofen transdermal, 25 nabumetone, superoxide dismutase (Chiron) and superoxide dismutase Enzon.

The compounds of the present invention will also be useful in treatment or prevention of angiogenesis-related disorders or conditions, for example, tumor growth, metastasis, macular degeneration, and atherosclerosis.

In a further embodiment, the present invention also provides therapeutic 30 combinations for the treatment or prevention of ophthalmic disorders or conditions

such as glaucoma. For example the present inventive compounds advantageously will be used in therapeutic combination with a drug which reduces the intraocular pressure of patients afflicted with glaucoma. Such intraocular pressure-reducing drugs include without limitation; latanoprost, travoprost, bimatoprost, or
5 unoprostol. The therapeutic combination of a compound of the present invention plus an intraocular pressure-reducing drug will be useful because each is believed to achieve its effects by affecting a different mechanism.

In another combination of the present invention, the present inventive compounds can be used in therapeutic combination with an antihyperlipidemic or
10 cholesterol-lowering drug such as a benzothiepine or a benzothiazepine antihyperlipidemic drug. Examples of benzothiepine antihyperlipidemic drugs useful in the present inventive therapeutic combination can be found in U.S. Patent No. 5,994,391, herein incorporated by reference. Some benzothiazepine antihyperlipidemic drugs are described in WO 93/16055. Alternatively, the
15 antihyperlipidemic or cholesterol-lowering drug useful in combination with a compound of the present invention can be an HMG Co-A reductase inhibitor. Examples of HMG Co-A reductase inhibitors useful in the present therapeutic combination include, individually, benfluorex, fluvastatin, lovastatin, provastatin, simvastatin, atorvastatin, cerivastatin, bervastatin, ZD-9720 (described in PCT
20 Patent Application No. WO 97/06802), ZD-4522 (CAS No. 147098-20-2 for the calcium salt; CAS No. 147098-18-8 for the sodium salt; described in European Patent No. EP 521471), BMS 180431 (CAS No. 129829-03-4), or NK-104 (CAS No. 141750-63-2). The therapeutic combination of a compound of the present invention plus an antihyperlipidemic or cholesterol-lowering drug will be useful, for
25 example, in reducing the risk of formation of atherosclerotic lesions in blood vessels. For example, atherosclerotic lesions often initiate at inflamed sites in blood vessels. It is established that antihyperlipidemic or cholesterol-lowering drug reduce risk of formation of atherosclerotic lesions by lowering lipid levels in blood. Without limiting the invention to a single mechanism of action, it is believed that
30 one way the compounds of the present combination will work in concert to provide

improved control of atherosclerotic lesions by, for example, reducing inflammation of the blood vessels in concert with lowering blood lipid levels.

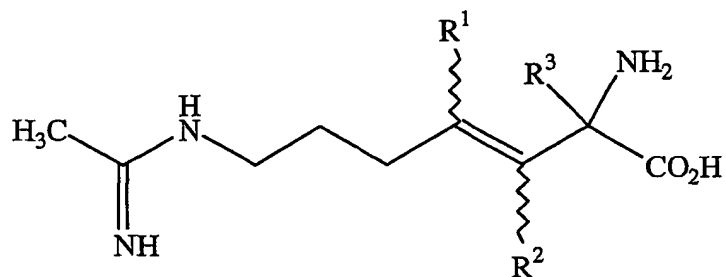
In another embodiment of the invention, the present compounds can be used in combination with other compounds or therapies for the treatment of central nervous conditions or disorders such as migraine. For example, the present compounds can be used in therapeutic combination with caffeine, a 5-HT-1B/1D agonist (for example, a triptan such as sumatriptan, naratriptan, zolmitriptan, rizatriptan, almotriptan, or frovatriptan), a dopamine D4 antagonist (e.g., sonopiprazole), aspirin, acetaminophen, ibuprofen, indomethacin, naproxen sodium, isometheptene, dichloralphenazone, butalbital, an ergot alkaloid (e.g., ergotamine, dihydroergotamine, bromocriptine, ergonovine, or methyl ergonovine), a tricyclic antidepressant (e.g., amitriptyline or nortriptyline), a serotonergic antagonist (e.g., methysergide or cyproheptadine), a beta-adrenergic antagonist (e.g., propranolol, timolol, atenolol, nadolol, or metoprolol), or a monoamine oxidase inhibitor (e.g., phenelzine or isocarboxazid).

A further embodiment provides a therapeutic combination of a compound of the present invention with an opioid compound. Opioid compounds useful in this combination include without limitation morphine, methadone, hydromorphone, oxymorphone, levorphanol, levallorphan, codeine, dihydrocodeine, dihydrohydroxycodone, pentazocine, hydrocodone, oxycodone, nalmefene, etorphine, levorphanol, fentanyl, sufentanil, DAMGO, butorphanol, buprenorphine, naloxone, naltrexone, CTOP, diprenorphine, beta-funaltrexamine, naloxonazine, nalorphine, pentazocine, nalbuphine, naloxone benzoylhydrazone, bremazocine, ethylketocyclazocine, U50,488, U69,593, spiradoline, nor-binaltorphimine, naltrindole, DPDPE, [D-1a², glu⁴]deltorphan, DSLET, met-enkephalin, leu-enkephalin, beta-endorphin, dynorphin A, dynorphin B, and alpha-neoendorphin. An advantage to the combination of the present invention with an opioid compound is that the present inventive compounds will allow a reduction in the dose of the opioid compound, thereby reducing the risk or severity of opioid side effects, such as opioid addiction.

Detailed Description of the Invention

In an embodiment represented by Formula I, the invention relates to:

5



I

or a pharmaceutically acceptable salt thereof, wherein:

or a pharmaceutically acceptable salt thereof, wherein:

10 R^1 is selected from the group consisting of hydrogen, halo, C_1 - C_5 alkyl and C_1 - C_5 alkyl substituted by alkoxy or one or more halo;

R^2 is selected from the group consisting of hydrogen, halo, C_1 - C_5 alkyl and C_1 - C_5 alkyl substituted by alkoxy or one or more halo;

R^3 is C_1 - C_5 alkyl or C_1 - C_5 alkyl substituted by alkoxy or one or more halo.

15 In one embodiment of the present invention represented by Formula I, the compound is the Z isomer.

In another embodiment of the present invention represented by Formula I, the compound is the E isomer.

20 In yet another embodiment of the present invention represented by Formula I, R^1 is hydrogen, halo, or C_1 - C_5 alkyl, said C_1 - C_5 alkyl optionally substituted by halo or alkoxy, said alkoxy optionally substituted by one or more halo; R^2 is hydrogen, halo or C_1 - C_5 alkyl, said C_1 - C_5 alkyl optionally substituted by halo or alkoxy, said alkoxy optionally substituted by one or more halo; and R^3 is C_1 - C_5 alkyl, said C_1 - C_5 alkyl optionally substituted by halo or alkoxy.

In another embodiment of the present invention represented by Formula I, R^1 is hydrogen, halo, or C_1 - C_3 alkyl; R^2 is hydrogen, halo or C_1 - C_3 alkyl; and R^3 is C_1 - C_5 alkyl, said C_1 - C_5 alkyl optionally substituted by fluorine or alkoxy.

In a further embodiment of the present invention represented by Formula I,
5 R^1 is hydrogen, halo, or C_1 - C_3 alkyl; R^2 is hydrogen, halo or C_1 - C_3 alkyl; and R^3 is C_1 - C_3 alkyl.

In another embodiment of the present invention represented by Formula I, R^1 is hydrogen; R^2 is hydrogen, halo or C_1 - C_3 alkyl; and R^3 is C_1 - C_3 alkyl.

In a still further embodiment of the present invention represented by
10 Formula I, R^1 is hydrogen; R^2 is hydrogen or halo; and R^3 is C_1 - C_3 alkyl.

In another embodiment of the present invention represented by Formula I, R^1 is hydrogen; R^2 is hydrogen or fluorine; and R^3 is C_1 - C_3 alkyl.

In another embodiment of the present invention represented by Formula I, R^1 is hydrogen; R^2 is hydrogen or fluorine; and R^3 is methyl.

15 In another embodiment of the present invention represented by Formula I, R^1 is hydrogen; R^2 is hydrogen; and R^3 is methyl.

In a further embodiment of the present invention represented by Formula I, R^1 is hydrogen; R^2 is fluorine; and R^3 is methyl.

In another embodiment of the present invention represented by Formula I,
20 R^1 is halo; R^2 is hydrogen, halo or C_1 - C_3 alkyl; and R^3 is C_1 - C_3 alkyl.

In a further embodiment of the present invention represented by Formula I, R^1 is halo; R^2 is halo; and R^3 is C_1 - C_3 alkyl.

In another embodiment of the present invention represented by Formula I, R^1 is fluorine; R^2 is fluorine; and R^3 is methyl.

25 In another embodiment of the present invention represented by Formula I, R^1 is fluorine; R^2 is hydrogen or C_1 - C_3 alkyl; and R^3 is methyl.

In a further embodiment of the present invention represented by Formula I, R^1 is fluorine; R^2 is hydrogen; and R^3 is methyl.

In another embodiment of the present invention represented by Formula I,
30 R^1 is methyl; R^2 is hydrogen; and R^3 is methyl.

In a further embodiment of the present invention represented by Formula I, R^1 is hydrogen; R^2 is methyl; and R^3 is methyl.

In another embodiment of the present invention represented by Formula I, R^1 is methyl; R^2 is methyl; and R^3 is methyl.

5 In yet another embodiment of the present invention represented by Formula I, R^1 is hydrogen, halo or C_1 - C_5 alkyl, said C_1 - C_5 alkyl optionally substituted by alkoxy or one or more fluorine; R^2 is hydrogen, halo or C_1 - C_5 alkyl, said C_1 - C_5 alkyl optionally substituted by alkoxy or one or more fluorine; and R^3 is methyl optionally substituted by one or more alkoxy or halo.

10 In a further embodiment of the present invention represented by Formula I, R^1 is hydrogen or fluorine; R^2 is C_1 - C_3 alkyl substituted by one or more halo; and R^3 is methyl.

In another embodiment of the present invention represented by Formula I, R^1 is hydrogen; R^2 is CH_2F ; and R^3 is methyl.

15 In still another embodiment of the present invention represented by Formula I, R^1 is CH_2F ; R^2 is hydrogen; and R^3 is methyl.

In a further embodiment of the present invention represented by Formula I, R^1 is hydrogen; R^2 is hydrogen; and R^3 is CH_2F .

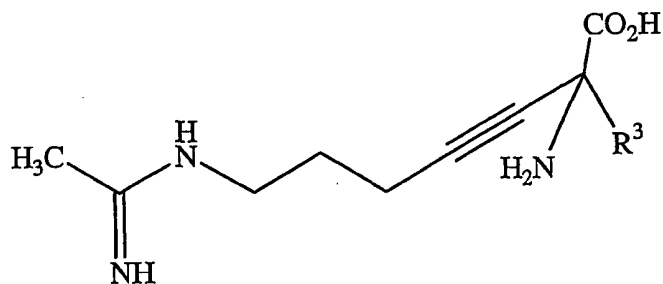
20 In another embodiment of the present invention represented by Formula I, R^1 is hydrogen; R^2 is methoxymethyl; and R^3 is methyl.

In a further embodiment of the present invention represented by Formula I, R^1 is methoxymethyl; R^2 is hydrogen; and R^3 is methyl.

In another embodiment of the present invention represented by Formula I, R^1 is hydrogen; R^2 is hydrogen; and R^3 is methoxymethyl.

25 In an embodiment represented by Formula II, the invention relates to:

21



II

or a pharmaceutically acceptable salt thereof, wherein:

- 5 R^3 is C_1 - C_5 alkyl, said C_1 - C_5 alkyl optionally substituted by halo or alkoxy, said alkoxy optionally substituted by one or more halo.

In another embodiment of the present invention represented by Formula II, R^3 is C_1 - C_5 alkyl substituted by one or more halo.

- 10 In a further embodiment of the present invention represented by Formula II, R^3 is C_1 - C_5 alkyl substituted by one or more fluorine.

In still another embodiment of the present invention represented by Formula II, R^3 is methyl substituted by one or more halo.

- 15 In yet another embodiment of the present invention represented by Formula II, R^3 is methyl substituted by one or more fluorine. In another embodiment of the present invention represented by Formula II, R^3 is CH_2F .

In still another embodiment of the present invention represented by Formula II, R^3 is C_1 - C_5 alkyl substituted by alkoxy.

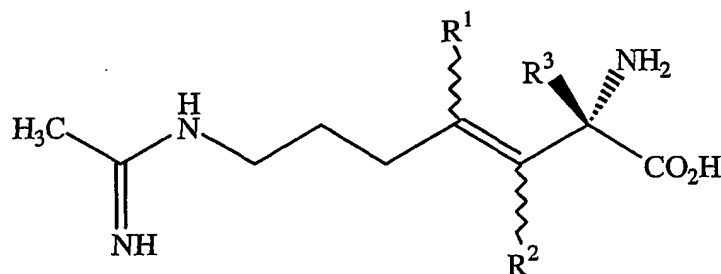
In a further embodiment of the present invention represented by Formula II, R^3 is methoxy methyl.

- 20 In yet another embodiment of the present invention represented by Formula II, R^3 is C_1 - C_5 alkyl.

In another embodiment of the present invention represented by Formula II, R^3 is methyl.

In an embodiment represented by Formula III, the invention relates to:

25



III

or a pharmaceutically acceptable salt thereof, wherein:

- 5 R^1 is selected from the group consisting of hydrogen, halo, C_1 - C_5 alkyl and C_1 - C_5 alkyl substituted by alkoxy or one or more halo;

R^2 is selected from the group consisting of hydrogen, halo, C_1 - C_5 alkyl and C_1 - C_5 alkyl substituted by alkoxy or one or more halo;

R^3 is C_1 - C_5 alkyl or C_1 - C_5 alkyl be substituted by alkoxy or one or more halo.

- 10 In one embodiment of the present invention represented by Formula III, the compound is the Z isomer.

In another embodiment of the present invention represented by Formula III, the compound is the E isomer.

- In yet another embodiment of the present invention represented by Formula
 15 III, R^1 is hydrogen, halo, or C_1 - C_5 alkyl, said C_1 - C_5 alkyl optionally substituted by halo or alkoxy, said alkoxy optionally substituted by one or more halo; R^2 is hydrogen, halo or C_1 - C_5 alkyl, said C_1 - C_5 alkyl optionally substituted by halo or alkoxy, said alkoxy optionally substituted by one or more halo; and R^3 is C_1 - C_5 alkyl, said C_1 - C_5 alkyl optionally substituted by halo or alkoxy.

- 20 In another embodiment of the present invention represented by Formula III, R^1 is hydrogen, halo, or C_1 - C_3 alkyl; R^2 is hydrogen, halo or C_1 - C_3 alkyl; and R^3 is C_1 - C_5 alkyl, said C_1 - C_5 alkyl optionally substituted by fluorine or alkoxy.

- In a further embodiment of the present invention represented by Formula III,
 25 R^1 is hydrogen, halo, or C_1 - C_3 alkyl; R^2 is hydrogen, halo or C_1 - C_3 alkyl; and R^3 is C_1 - C_3 alkyl.

In another embodiment of the present invention represented by Formula III, R^1 is hydrogen; R^2 is hydrogen, halo or C_1 - C_3 alkyl; and R^3 is C_1 - C_3 alkyl.

In a still further embodiment of the present invention represented by Formula III, R^1 is hydrogen; R^2 is hydrogen or halo; and R^3 is C_1 - C_3 alkyl.

5 In another embodiment of the present invention represented by Formula III, R^1 is hydrogen; R^2 is hydrogen or fluorine; and R^3 is C_1 - C_3 alkyl.

In another embodiment of the present invention represented by Formula III, R^1 is hydrogen; R^2 is hydrogen or fluorine; and R^3 is methyl.

In another embodiment of the present invention represented by Formula III,
10 R^1 is hydrogen; R^2 is hydrogen; and R^3 is methyl.

In a further embodiment of the present invention represented by Formula III, R^1 is hydrogen; R^2 is fluorine; and R^3 is methyl.

In another embodiment of the present invention represented by Formula III, R^1 is halo; R^2 is hydrogen, halo or C_1 - C_3 alkyl; and R^3 is C_1 - C_3 alkyl.

15 In a further embodiment of the present invention represented by Formula III, R^1 is halo; R^2 is halo; and R^3 is C_1 - C_3 alkyl.

In another embodiment of the present invention represented by Formula III, R^1 is fluorine; R^2 is fluorine; and R^3 is methyl.

In another embodiment of the present invention represented by Formula III,
20 R^1 is fluorine; R^2 is hydrogen or C_1 - C_3 alkyl; and R^3 is methyl.

In a further embodiment of the present invention represented by Formula III, R^1 is fluorine; R^2 is hydrogen; and R^3 is methyl.

In another embodiment of the present invention represented by Formula III, R^1 is methyl; R^2 is hydrogen; and R^3 is methyl.

25 In a further embodiment of the present invention represented by Formula III, R^1 is hydrogen; R^2 is methyl; and R^3 is methyl.

In another embodiment of the present invention represented by Formula III, R^1 is methyl; R^2 is methyl; and R^3 is methyl.

In yet another embodiment of the present invention represented by Formula
30 III, R^1 is hydrogen, halo or C_1 - C_5 alkyl, said C_1 - C_5 alkyl optionally substituted by

alkoxy or one or more fluorine; R^2 is hydrogen, halo or C_1 - C_5 alkyl, said C_1 - C_5 alkyl optionally substituted by alkoxy or one or more fluorine; and R^3 is methyl optionally substituted by one or more alkoxy or halo.

In a further embodiment of the present invention represented by Formula III,
 5 R^1 is hydrogen or fluorine; R^2 is C_1 - C_3 alkyl substituted by one or more halo; and R^3 is methyl.

In another embodiment of the present invention represented by Formula III, R^1 is hydrogen; R^2 is CH_2F ; and R^3 is methyl.

In still another embodiment of the present invention represented by Formula
 10 III, R^1 is CH_2F ; R^2 is hydrogen; and R^3 is methyl.

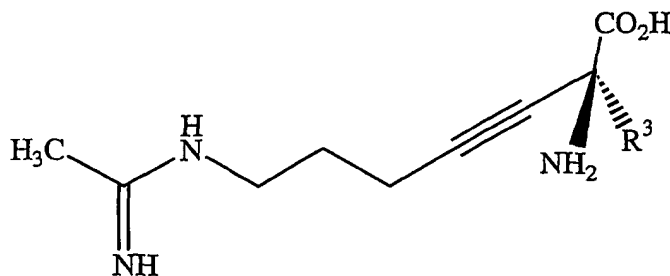
In a further embodiment of the present invention represented by Formula III, R^1 is hydrogen; R^2 is hydrogen; and R^3 is CH_2F .

In another embodiment of the present invention represented by Formula III, R^1 is hydrogen; R^2 is methoxymethyl; and R^3 is methyl.

15 In a further embodiment of the present invention represented by Formula III, R^1 is methoxymethyl; R^2 is hydrogen; and R^3 is methyl.

In another embodiment of the present invention represented by Formula III, R^1 is hydrogen; R^2 is hydrogen; and R^3 is methoxymethyl.

20 In an embodiment represented by Formula IV, the invention relates to:



IV

or a pharmaceutically acceptable salt thereof, wherein:

25 R^3 is C_1 - C_5 alkyl, said C_1 - C_5 alkyl optionally substituted by halo or alkoxy, said alkoxy optionally substituted by one or more halo.

In another embodiment of the present invention represented by Formula II, R^3 is C_1 - C_5 alkyl substituted by one or more halo.

In a further embodiment of the present invention represented by Formula II, R^3 is C_1 - C_5 alkyl substituted by one or more fluorine.

5 In still another embodiment of the present invention represented by Formula II, R^3 is methyl substituted by one or more halo.

In yet another embodiment of the present invention represented by Formula II, R^3 is methyl substituted by one or more fluorine. In another embodiment of the present invention represented by Formula II, R^3 is CH_2F .

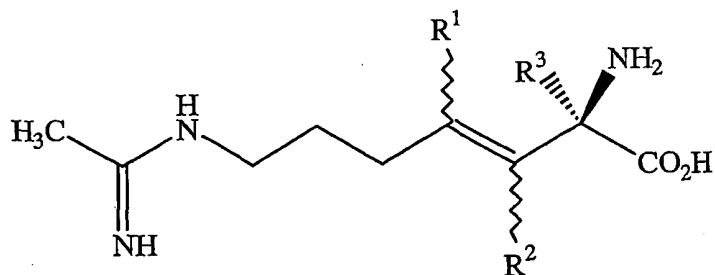
10 In still another embodiment of the present invention represented by Formula II, R^3 is C_1 - C_5 alkyl substituted by alkoxy.

In a further embodiment of the present invention represented by Formula II, R^3 is methoxy methyl.

In yet another embodiment of the present invention represented by Formula
15 II, R^3 is C_1 - C_5 alkyl.

In another embodiment of the present invention represented by Formula II, R^3 is methyl.

20 In an embodiment represented by Formula V, the invention relates to:



V

25 or a pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from the group consisting of hydrogen, halo, C_1 - C_5 alkyl and C_1 - C_5 alkyl substituted by alkoxy or one or more halo;

R^2 is selected from the group consisting of hydrogen, halo, C_1 - C_5 alkyl and C_1 - C_5 alkyl substituted by alkoxy or one or more halo;

- 5 R^3 is C_1 - C_5 alkyl or C_1 - C_5 alkyl be substituted by alkoxy or one or more halo.

In one embodiment of the present invention represented by Formula V, the compound is the Z isomer.

In another embodiment of the present invention represented by Formula V, the compound is the E isomer.

- 10 In yet another embodiment of the present invention represented by Formula V, R^1 is hydrogen, halo, or C_1 - C_5 alkyl, said C_1 - C_5 alkyl optionally substituted by halo or alkoxy, said alkoxy optionally substituted by one or more halo; R^2 is hydrogen, halo or C_1 - C_5 alkyl, said C_1 - C_5 alkyl optionally substituted by halo or alkoxy, said alkoxy optionally substituted by one or more halo; and R^3 is C_1 - C_5 alkyl, said C_1 - C_5 alkyl optionally substituted by halo or alkoxy.

In another embodiment of the present invention represented by Formula V, R^1 is hydrogen, halo, or C_1 - C_3 alkyl; R^2 is hydrogen, halo or C_1 - C_3 alkyl; and R^3 is C_1 - C_5 alkyl, said C_1 - C_5 alkyl optionally substituted by fluorine or alkoxy.

- 20 In a further embodiment of the present invention represented by Formula V, R^1 is hydrogen, halo, or C_1 - C_3 alkyl; R^2 is hydrogen, halo or C_1 - C_3 alkyl; and R^3 is C_1 - C_3 alkyl.

In another embodiment of the present invention represented by Formula V, R^1 is hydrogen; R^2 is hydrogen, halo or C_1 - C_3 alkyl; and R^3 is C_1 - C_3 alkyl.

- 25 In a still further embodiment of the present invention represented by Formula V, R^1 is hydrogen; R^2 is hydrogen or halo; and R^3 is C_1 - C_3 alkyl.

In another embodiment of the present invention represented by Formula V, R^1 is hydrogen; R^2 is hydrogen or fluorine; and R^3 is C_1 - C_3 alkyl.

In another embodiment of the present invention represented by Formula V, R^1 is hydrogen; R^2 is hydrogen or fluorine; and R^3 is methyl.

In another embodiment of the present invention represented by Formula V, R^1 is hydrogen; R^2 is hydrogen; and R^3 is methyl.

In a further embodiment of the present invention represented by Formula V, R^1 is hydrogen; R^2 is fluorine; and R^3 is methyl.

5 In another embodiment of the present invention represented by Formula V, R^1 is halo; R^2 is hydrogen, halo or C_1 - C_3 alkyl; and R^3 is C_1 - C_3 alkyl.

In a further embodiment of the present invention represented by Formula V, R^1 is halo; R^2 is halo; and R^3 is C_1 - C_3 alkyl.

10 In another embodiment of the present invention represented by Formula V, R^1 is fluorine; R^2 is fluorine; and R^3 is methyl.

In another embodiment of the present invention represented by Formula V, R^1 is fluorine; R^2 is hydrogen or C_1 - C_3 alkyl; and R^3 is methyl.

In a further embodiment of the present invention represented by Formula V, R^1 is fluorine; R^2 is hydrogen; and R^3 is methyl.

15 In another embodiment of the present invention represented by Formula V, R^1 is methyl; R^2 is hydrogen; and R^3 is methyl.

In a further embodiment of the present invention represented by Formula V, R^1 is hydrogen; R^2 is methyl; and R^3 is methyl.

20 In another embodiment of the present invention represented by Formula V, R^1 is methyl; R^2 is methyl; and R^3 is methyl.

In yet another embodiment of the present invention represented by Formula V, R^1 is hydrogen, halo or C_1 - C_5 alkyl, said C_1 - C_5 alkyl optionally substituted by alkoxy or one or more fluorine; R^2 is hydrogen, halo or C_1 - C_5 alkyl, said C_1 - C_5 alkyl optionally substituted by alkoxy or one or more fluorine; and R^3 is methyl
25 optionally substituted by one or more alkoxy or halo.

In a further embodiment of the present invention represented by Formula V, R^1 is hydrogen or fluorine; R^2 is C_1 - C_3 alkyl substituted by one or more halo; and R^3 is methyl.

30 In another embodiment of the present invention represented by Formula V, R^1 is hydrogen; R^2 is CH_2F ; and R^3 is methyl.

In still another embodiment of the present invention represented by Formula V, R^1 is CH_2F ; R^2 is hydrogen; and R^3 is methyl.

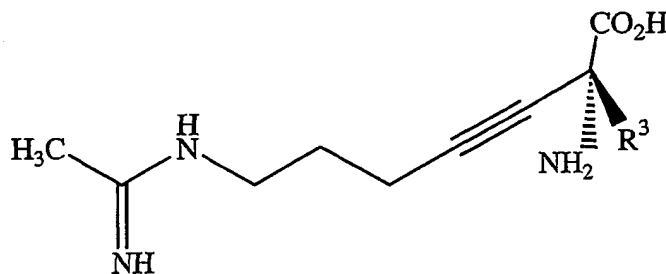
In a further embodiment of the present invention represented by Formula V, R^1 is hydrogen; R^2 is hydrogen; and R^3 is CH_2F .

5 In another embodiment of the present invention represented by Formula V, R^1 is hydrogen; R^2 is methoxymethyl; and R^3 is methyl.

In a further embodiment of the present invention represented by Formula V, R^1 is methoxymethyl; R^2 is hydrogen; and R^3 is methyl.

In another embodiment of the present invention represented by Formula V, R^1 is
10 hydrogen; R^2 is hydrogen; and R^3 is methoxymethyl.

In an embodiment represented by Formula VI, the invention relates to:



15

VI

or a pharmaceutically acceptable salt thereof, wherein:

R^3 is $\text{C}_1\text{-C}_5$ alkyl, said $\text{C}_1\text{-C}_5$ alkyl optionally substituted by halo or alkoxy, said alkoxy optionally substituted by one or more halo.

20 In another embodiment of the present invention represented by Formula VI, R^3 is $\text{C}_1\text{-C}_5$ alkyl substituted by one or more halo.

In a further embodiment of the present invention represented by Formula VI, R^3 is $\text{C}_1\text{-C}_5$ alkyl substituted by one or more fluorine.

In still another embodiment of the present invention represented by Formula
25 VI, R^3 is methyl substituted by one or more halo.

In yet another embodiment of the present invention represented by Formula VI, R^3 is methyl substituted by one or more fluorine. In another embodiment of the present invention represented by Formula VI, R^3 is CH_2F .

In still another embodiment of the present invention represented by Formula
5 VI, R^3 is C_1 - C_5 alkyl substituted by alkoxy.

In a further embodiment of the present invention represented by Formula VI, R^3 is methoxy methyl.

In yet another embodiment of the present invention represented by Formula VI, R^3 is C_1 - C_5 alkyl.

10 In another embodiment of the present invention represented by Formula VI, R^3 is methyl.

The present invention also includes pharmaceutical compositions that comprise a compound of Formula I, II, III, IV, V, or VI.

Methods of using the compounds of Formula I, II, III, IV, V, or VI include
15 the use of inhibiting nitric oxide synthesis in a subject in need of such inhibition by administering a therapeutically effective amount of the present compound, selectively inhibiting nitric oxide synthesis produced by inducible nitric oxide synthase over nitric oxide produced by the constitutive forms of nitric oxide synthase in a subject in need of such inhibition by administering a therapeutically
20 effective amount of a compound of Formula I, II, III, IV, V, or VI, lowering nitric oxide levels in a subject in need of such by administering a therapeutically effective amount of a compound of Formula I, II, III, IV, V, or VI, lowering nitric oxide levels in a subject in need of such by administering a therapeutically effective amount of a pharmaceutical composition comprising a compound of Formula I, II,
25 III, IV, V, or VI.

The compounds of the present invention may also be used advantageously in combination with a second pharmaceutically active substance, particularly in combination with a selective inhibitor of the inducible isoform of cyclooxygenase (COX-2). Thus, in a further aspect of the invention there is provided the use of a
30 present compound or a pharmaceutically acceptable salt thereof, in combination

with a COX-2 inhibitor for the treatment of inflammation, inflammatory disease and inflammatory related disorders. And there is also provided a method of treating, or reducing the risk of, inflammation, inflammatory disease and inflammatory related disorders in a person suffering from or at risk of, said disease or condition, wherein
5 the method comprises administering to the person a therapeutically effective amount of a present compound or a pharmaceutically acceptable salt, thereof in combination with a COX-2 inhibitor. COX-2 inhibitors are illustrated but not limited by Celecoxib Vioxx. The NOS inhibitor and the COX-2 inhibitor may either be formulated together within the same pharmaceutical composition for
10 administration in a single dosage unit, or each component may be individually formulated such that separate dosages may be administered either simultaneously or sequentially.

The term "alkyl", alone or in combination, means an acyclic alkyl radical,
15 linear or branched, containing from 1 to 5, or from 1 to 3 carbon atoms. Said alkyl radicals may be optionally substituted with one or more halo.

The terms "alkoxy" embraces linear or branched oxy-containing radicals each having alkyl portions of one to five carbon atoms, such as methoxy radical. Examples of such radicals include methoxy, ethoxy, propoxy, butoxy and *tert*-
20 butoxy alkyls.

The term "halo" means halogens such as fluorine, chlorine, bromine or iodine atoms.

Also included in the family of compounds of Formula I, II, III, IV, V, or VI are the pharmaceutically-acceptable salts thereof. The term "pharmaceutically-
25 acceptable salts" embraces salts commonly used to form alkali metal salts and to form addition salts of free acids or free bases. The nature of the salt is not critical, provided that it is pharmaceutically acceptable. Suitable pharmaceutically-acceptable acid addition salts of compounds of Formula I, II, III, IV, V, or VI may be prepared from inorganic acid or from an organic acid. Examples of such
30 inorganic acids are hydrochloric, hydrobromic, hydroiodic, nitric, carbonic, sulfuric

and phosphoric acid. Appropriate organic acids may be selected from aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic and sulfonic classes of organic acids, examples of which are formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, mesylic, salicylic, p-hydroxybenzoic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethylsulfonic, benzenesulfonic, sulfanilic, stearic, cyclohexylaminosulfonic, algenic, galacturonic acid. Suitable pharmaceutically-acceptable base addition salts of compounds of Formula I, II, III, IV, V, or VI include metallic salts made from aluminum, calcium, lithium, magnesium, potassium, sodium and zinc or organic salts made from N,N'-dibenzylethylenediamine, choline, chlorprocaine, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procain. All of these salts may be prepared by conventional means from the corresponding compound of Formula I, II, III, IV, V, or VI by reacting, for example, the appropriate acid or base with the compound of Formula I, II, III, IV, V, or VI.

Although nitrogen protecting groups are illustratively shown as, *t*-butoxycarbonyl, or *t*-BOC, any suitable nitrogen protecting group could be substituted in the synthesis of the compounds of the present invention. Numerous protected amino groups useful in the present invention for are described by Theodora W. Greene and Peter G.M. Wuts (Protective Groups in Organic Synthesis, 3rd ed., John Wiley & Sons, New York, 1999, pp. 494-653). For example NZ can be a 4-chlorobenzylimino group. In one embodiment of the present invention, the protected amino group is any such group resulting from the reaction of an aldehyde with the corresponding amino group to form a Schiff base. A large variety of deprotecting reagents can be advantageously used in the present invention to effect the conversion of the intermediate to the desired compound. Many such deprotecting reagents are described by Greene and Wuts, *supra*. For example, when the protected amino group is a 4-chlorobenzylimino group or a *t*-butoxycarbonylamino group, preferably the deprotecting reagent is an acid. Some useful acid deprotecting agents include, without limitation, hydrochloric acid,

hydrobromic acid, sulfuric acid, trifluoroacetic acid, phosphoric acid, phosphorus acid, and acetic acid.

When a compound is described by both a structure and a name, the name is intended to correspond to the indicated structure, and similarly the structure is
5 intended to correspond with the indicated name.

While it may be possible for the compounds of Formula I, II, III, IV, V, or VI to be administered as the raw chemical, it is preferable to present them as a pharmaceutical composition. According to a further aspect, the present invention provides a pharmaceutical composition comprising a compound of Formula I, II, III,
10 IV, V, or VI or a pharmaceutically acceptable salt or solvate thereof, together with one or more pharmaceutically acceptable carriers thereof and optionally one or more other therapeutic ingredients. The carrier(s) must be acceptable in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

15 The formulations include those suitable for oral, parenteral (including subcutaneous, intradermal, intramuscular, intravenous and intraarticular), rectal and topical (including dermal, buccal, sublingual and intraocular) administration although the most suitable route may depend upon for example the condition and disorder of the recipient. The formulations may conveniently be presented in unit
20 dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing into association a compound of Formula I, II, III, IV, V, or VI or a pharmaceutically acceptable salt or solvate thereof with the carrier, which constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into
25 association the active ingredient with liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a
30 solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-

in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing
5 in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, lubricating, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be
10 formulated so as to provide slow or controlled release of the active ingredient therein.

Formulations for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the
15 intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example, saline, water-for-injection,
20 immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

Formulations for rectal administration may be presented as a suppository with the usual carriers such as cocoa butter or polyethylene glycol.

25 Formulations for topical administration in the mouth, for example buccally or sublingually, include lozenges comprising the active ingredient in a flavored basis such as sucrose and acacia or tragacanth, and pastilles comprising the active ingredient in a basis such as gelatin and glycerin or sucrose and acacia.

Preferred unit dosage formulations are those containing an effective dose, as
30 herein below recited, or an appropriate fraction thereof, of the active ingredient.

It should be understood that in addition to the ingredients particularly mentioned above, the formulations of this invention may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavoring agents.

5 The compounds of the invention may be administered orally or via injection at a dose of from 0.001 to 2500 mg/kg per day. The dose range for adult humans is generally from 0.005 mg to 10 g/day. Tablets or other forms of presentation provided in discrete units may conveniently contain an amount of compound of the invention which is effective at such dosage or as a multiple of the same, for
10 instance, units containing 0.5 mg to 200 mg, usually around 0.5 mg to 100 mg.

 The compounds of Formula I, II, III, IV, V, or VI are preferably administered orally or by injection (intravenous or subcutaneous). The precise amount of compound administered to a patient will be the responsibility of the attendant physician. However, the dose employed will depend on a number of
15 factors, including the age and sex of the patient, the precise disorder being treated, and its severity. Also, the route of administration may vary depending on the condition and its severity.

 Compounds of the present invention can exist in tautomeric, geometric or stereoisomeric forms. The present invention contemplates all such compounds,
20 including cis- and trans-geometric isomers and mixtures thereof, E- and Z-geometric isomers and mixtures thereof, R- and S-enantiomers, diastereomers, d-isomers, l-isomers, the racemic mixtures thereof and other mixtures thereof, as falling within the scope of the invention. Pharmaceutically acceptable salts of such tautomeric, geometric or stereoisomeric forms are also included within the
25 invention.

 The terms "cis" and "trans" denote a form of geometric isomerism in which two carbon atoms connected by a double bond will each have two highest ranking groups on the same side of the double bond ("cis" or "Z") or on opposite sides of the double bond ("trans" or "E"). Some of the compounds described contain
30 alkenyl groups, and are meant to include both cis and trans or "E" and "Z"

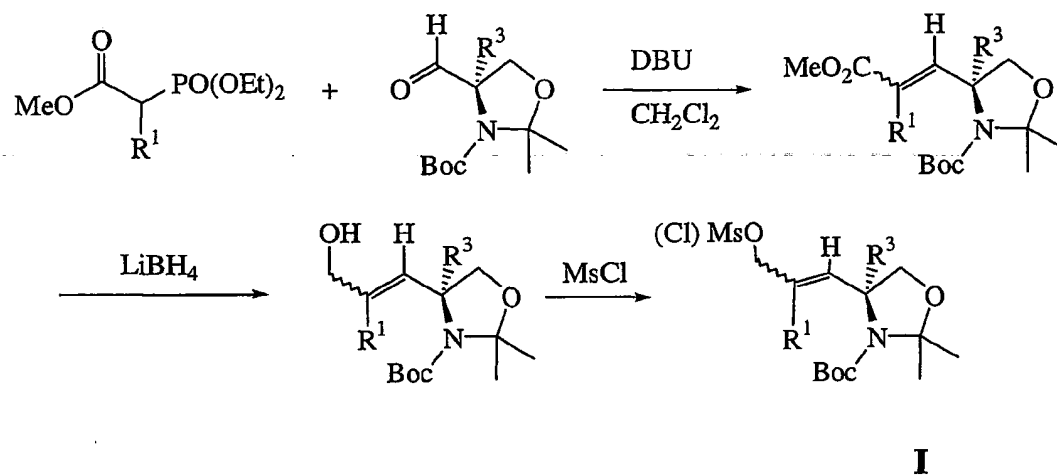
geometric forms. Other compounds of the invention include mixtures of both the *cis*/*Z* and the *trans*/*E* isomers.

The compounds described contain a stereocenter and are meant to include R, S, and mixtures of R and S forms. Some of the compounds described contain
 5 geometric isomers and are meant to include E, Z and mixtures of E and Z forms for each stereocenter present.

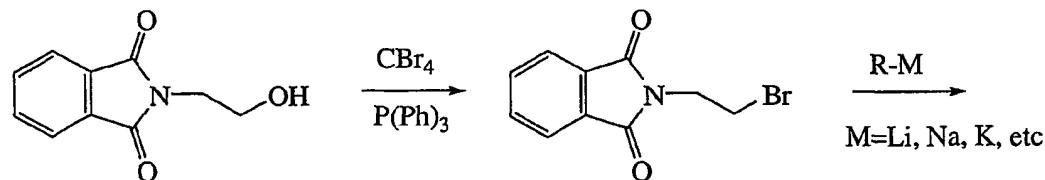
The following general synthetic sequences are useful in making the present invention.

10

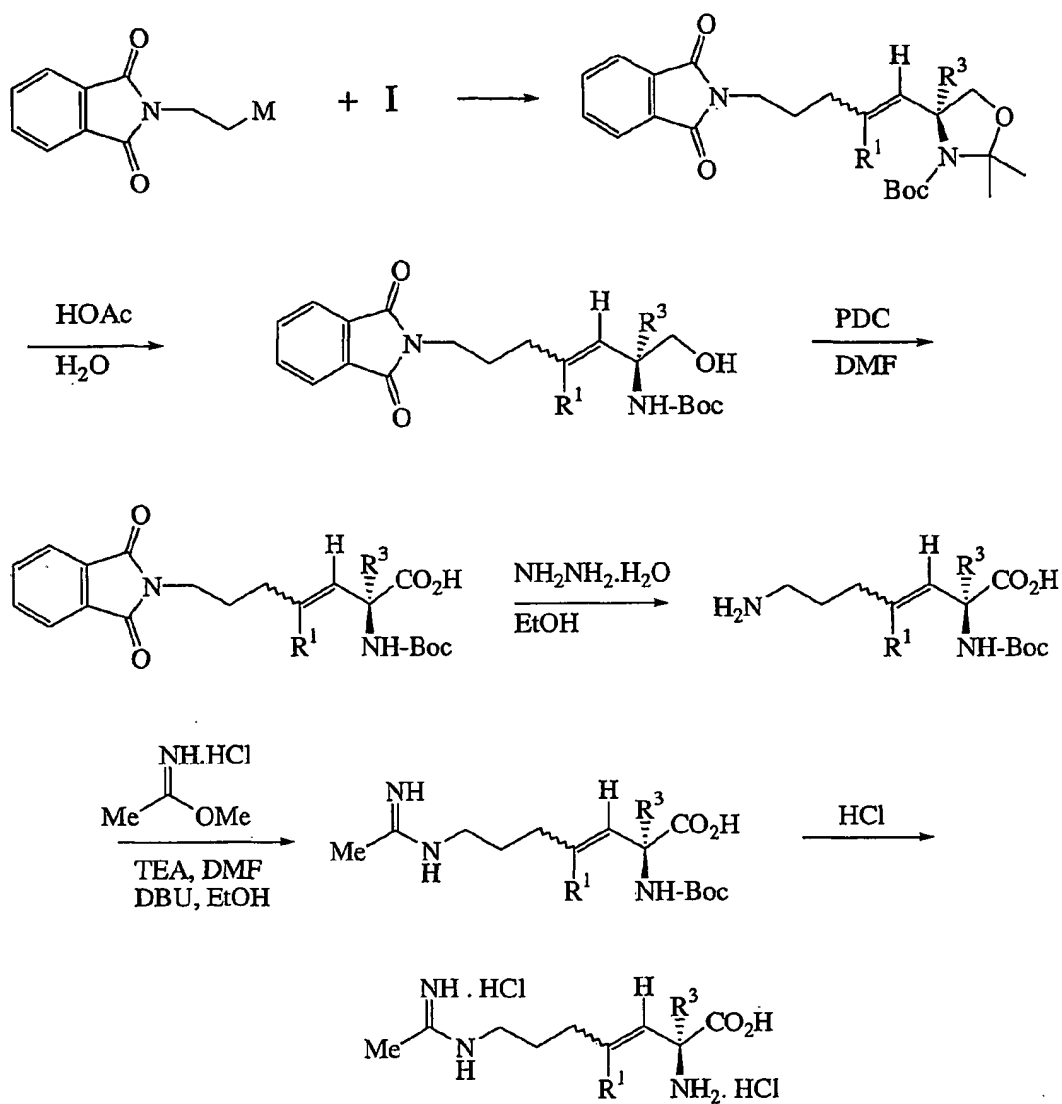
Scheme 1



15

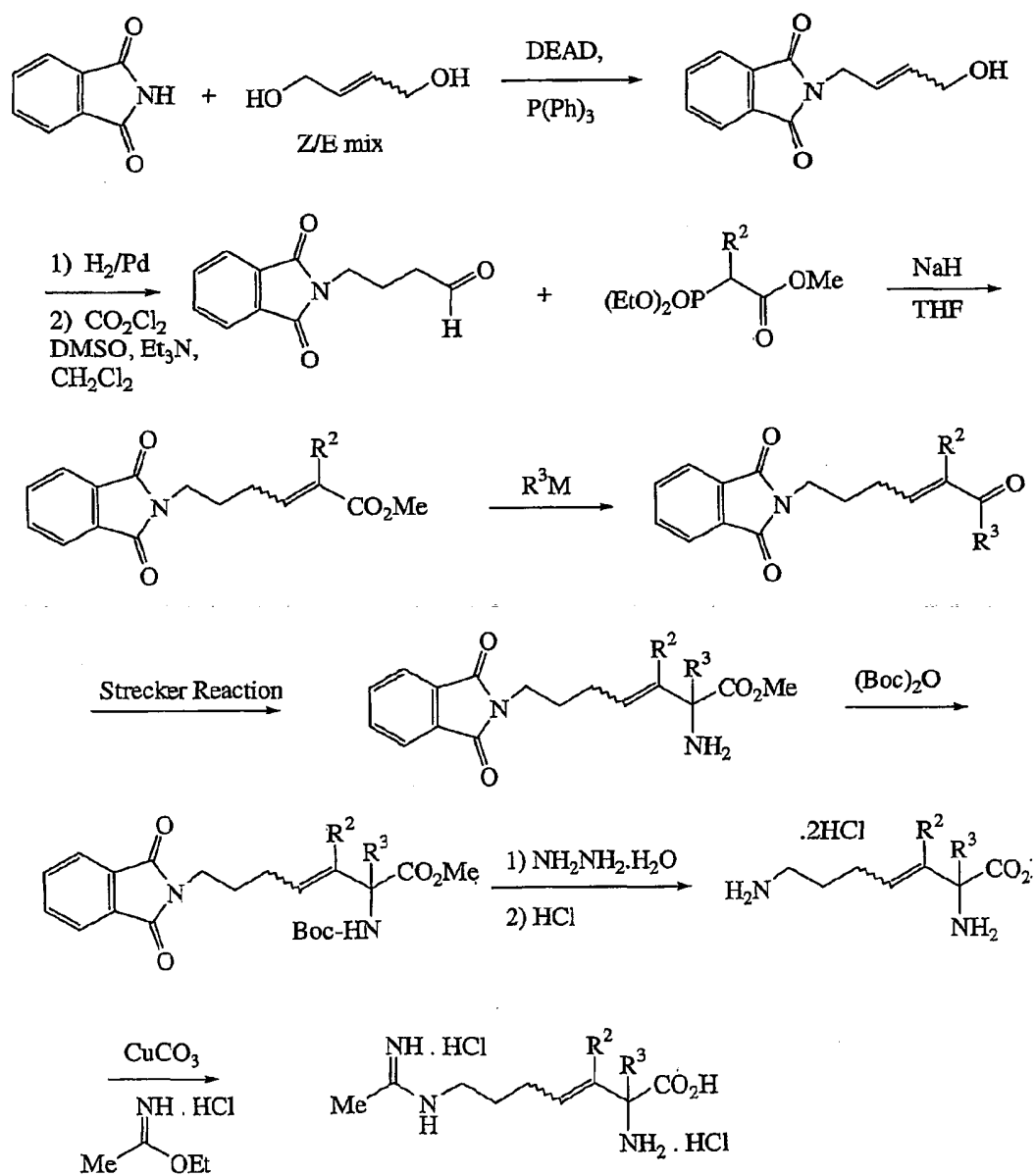


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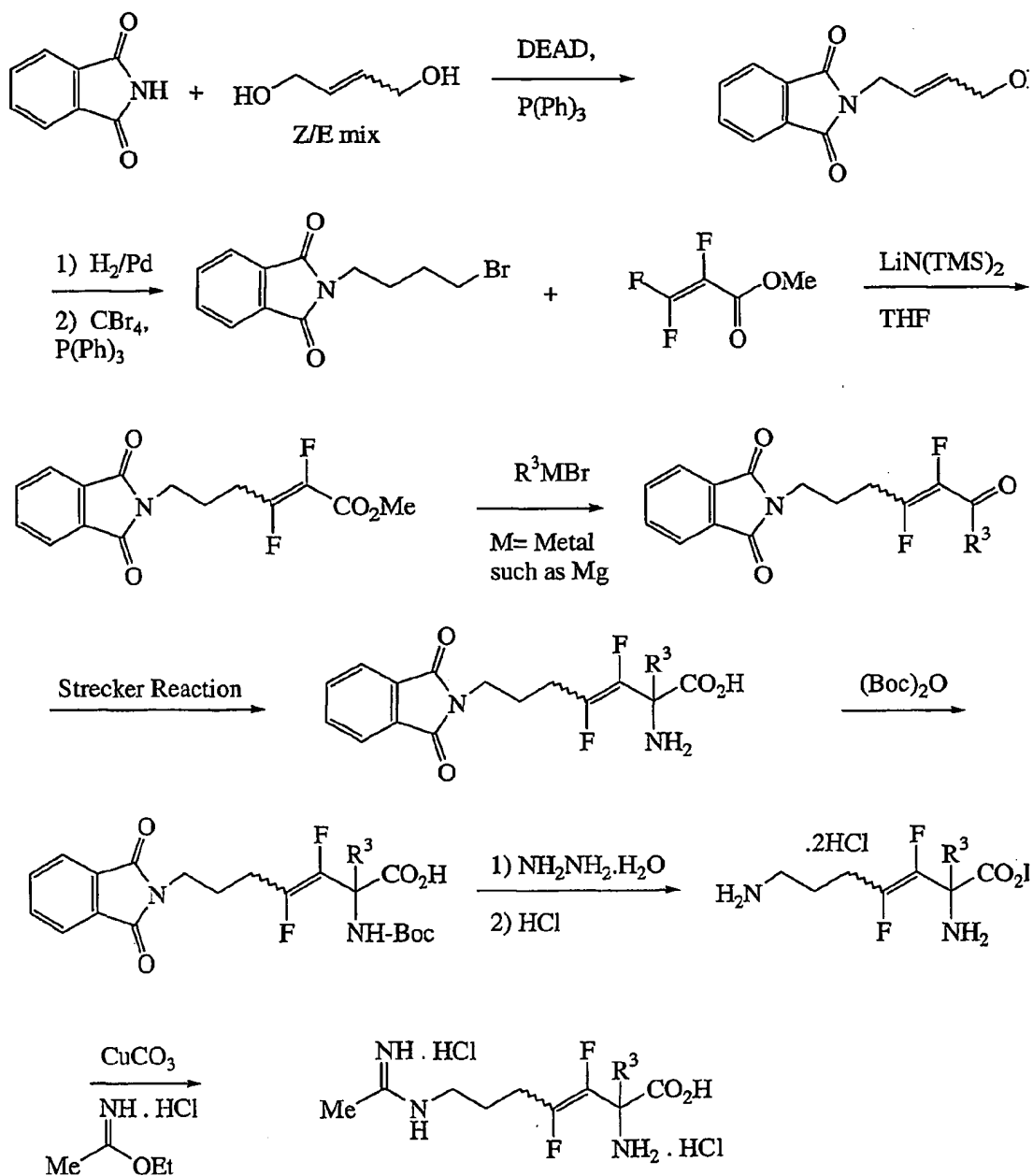


37

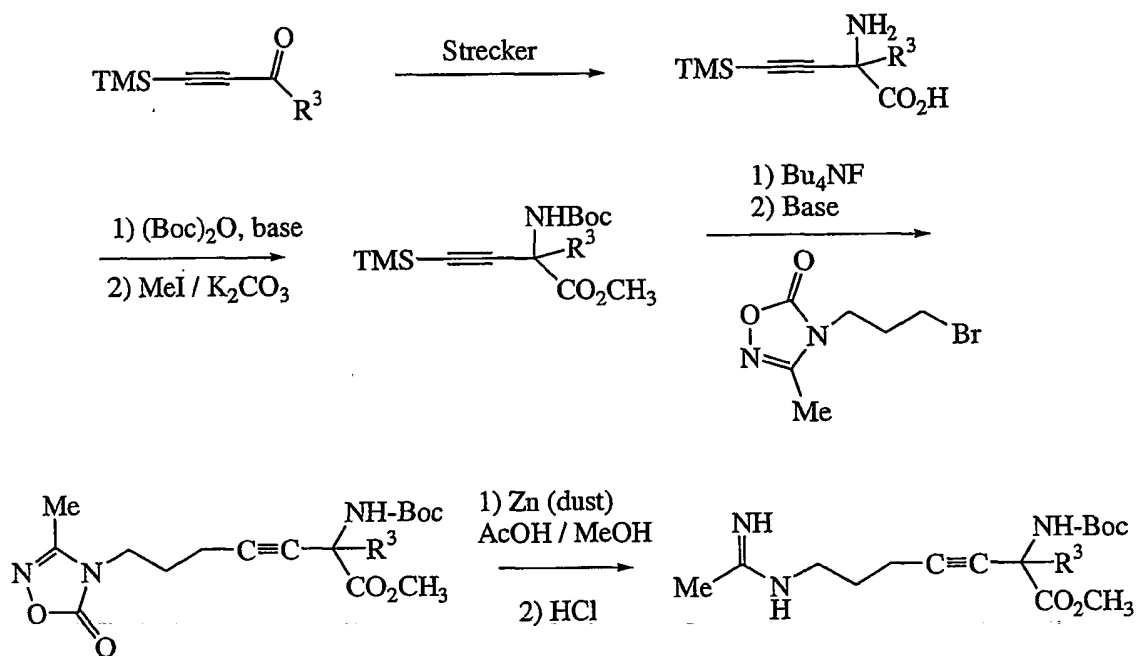
Scheme 2



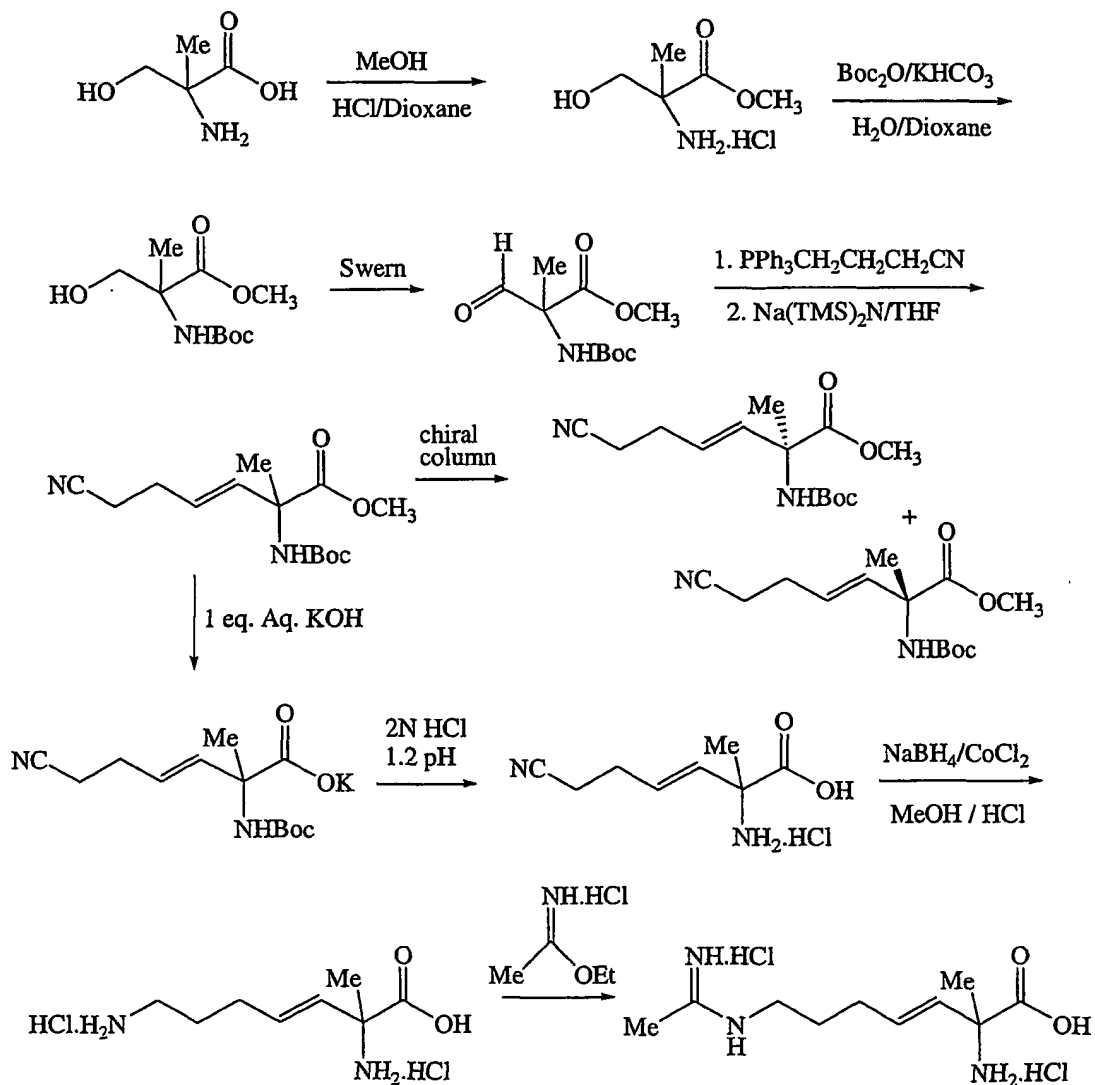
Scheme 3



Scheme 4



Scheme 5

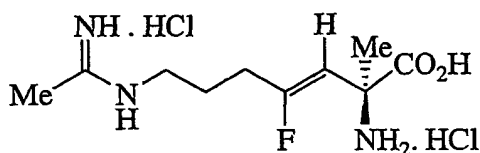


5

The following examples are provided to illustrate the present invention and are not intended to limit the scope thereof. Those skilled in the art will readily understand that known variations of the conditions and processes of the following preparative procedures can be used to prepare these compounds.

Example 1

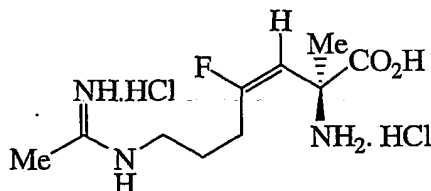
(2*S*,3*Z*)-2-amino-2-methyl-4-fluoro-7-[(1-iminoethyl)amino]-3-heptenoic acid,
dihydrochloride



5

Example 2

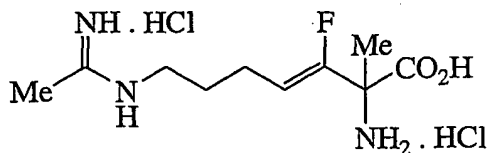
(2*S*,3*E*)-2-amino-2-methyl-4-fluoro-7-[(1-iminoethyl)amino]-3-heptenoic acid,
dihydrochloride



15

Example 3

(3*Z*)-2-amino-2-methyl-3-fluoro-7-[(1-iminoethyl)amino]-3-heptenoic acid,
dihydrochloride

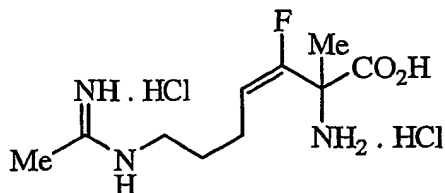


20

Example 4

42

(3E)-2-amino-2-methyl-3-fluoro-7-[(1-iminoethyl)amino]-3-heptenoic acid,
dihydrochloride

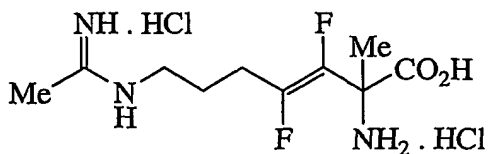


5

Example 5

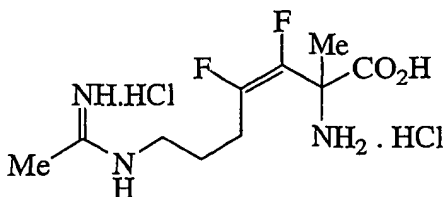
(3E)- 2-amino-2-methyl-3,4-difluoro-7-[(1-iminoethyl)amino]- 3-heptenoic acid,
dihydrochloride

10



Example 6

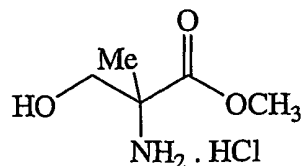
15 (3Z)- 2-amino-2-methyl-3,4-difluoro-7-[(1-iminoethyl)amino]- 3-heptenoic acid,
dihydrochloride



20 Example 7

Methyl 2-methylserinate hydrochloride

43



A sample of 2-methylserine (35.0 g, 0.2936 mol) was suspended in methanol (300 mL) in a three neck 1L round bottom flask maintained under argon. To this mixture
 5 was added 4N HCl/dioxane (85 mL) and the reaction mixture was stirred at 25 °C for 16 h. The reaction mixture became a clear colorless solution. Dry HCl gas was bubbled into the reaction mixture for 5 min. and the reaction mixture was then stirred at 60 °C for 4 h. It was then cooled and the excess of reagent/solvent was removed with a rotary evaporator at 65 °C to 70 °C to give the desired title product
 10 (yield 48.2 g, 96%) as a yellow sticky oil.

Elemental analyses Calcd for $C_5H_{11}NO_3 \cdot HCl$: C, 35.41; H, 7.13; N, 8.26; Cl, 20.90. Found for $C_5H_{11}NO_3 + 1.1 HCl + 1.0 H_2O$: C, 31.62; H, 7.58; N, 7.52; Cl, 19.97

15 IR (Neat, λ max cm^{-1}): 2959, 1739, 1591

1H NMR (D_2O , δ ppm): 1.52 (s, 3H), 3.75 (d, 1H), 3.87 (s, 3H), 4.05 (d, 1H)

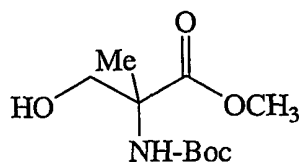
^{13}C NMR (D_2O , δ ppm): 20.63, 56.77, 64.47, 67.19, 174.24

Mass (M^{+1}) = 134

20

Example 8

Methyl N-(tert-butoxycarbonyl)-2-methylserinate



25

The product of **Example 7** (16.9 g, 0.1 mol) was dissolved in dioxane/water (120/60 mL) mixture to get a clear colorless solution. To this KHCO_3 (20.0 g, 0.2 mol) was added carefully to avoid excess foaming. The reaction mixture was then stirred for 10 min. at 25 °C followed by the addition of Boc_2O (24.0 g, 0.11 mol) and stirring for 24 h at 25 °C. The layers were then separated and the upper layer was taken up into EtOAc (200 mL). The lower aqueous layer was extracted with EtOAc (2 x 40 mL). Both organic layers were combined and dried over anhydrous MgSO_4 , filtered over celite and evaporated on a rotary evaporator at 60 °C to give a clear colorless oil. This was purified by column chromatography using 30% EtOAc in hexane to give the desired product as a white solid (18.0 g, 77%).

Elemental analyses Calcd for $\text{C}_{10}\text{H}_{19}\text{NO}_5$: C, 51.49; H, 8.21; N, 6.00. Found: C, 50.82; H, 8.25; N, 5.32

IR (Neat, λ max cm^{-1}): 2979, 1702, 1499

^1H NMR (CDCl_3 δ ppm): 1.45 (s, 9H), 1.48 (s, 3H), 3.4 (bs, 1H), 3.8 (s, 3H), 3.95 (m, 2H), 5.3 (bs, 1H)

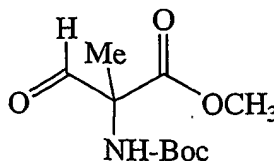
^{13}C NMR (CDCl_3 , δ ppm): 20.84, 27.40, 27.69, 28.25, 52.74, 66.96, 155.34, 173.91

Mass (M^{+1}) = 234

20

Example 9

Methyl 2-[(tert-butoxycarbonyl)amino]-2-methyl-3-oxopropanoate



25

To a stirred solution of oxalyl chloride (2.93 g, 0.0231 mol) in CH_2Cl_2 (30 mL) at -60 °C was added DMSO (3.6 g, 0.0462 mol) when the reaction temperature rose up to -55 °C. The reaction mixture was stirred at this temperature for 10 min. followed

by the addition of a solution of the product of **Example 8** (2.7 g, 0.01157 mol) in CH_2Cl_2 (20 mL) at -60°C . The reaction mixture was stirred for additional 20 min., quenched with Et_3N (5.85 g, 0.0578 mol) between -60°C to -30°C and filtered. DI water (50 mL) and EtOAc (100 mL) was added to the filtrate and the layers were
5 separated. The organic layer was dried over anhydrous MgSO_4 , filtered over Celite and concentrated on a rotary evaporator to give the crude product yellow oil. It was purified by column chromatography using 30% EtOAc in hexane as eluent to give the title product (1.39 g, 49%).

10 Elemental analyses Calcd for $\text{C}_{10}\text{H}_{17}\text{NO}_5$: C, 51.94; H, 7.41; N, 6.06. Found for $\text{C}_{10}\text{H}_{17}\text{NO}_5 + 0.3 \text{H}_2\text{O}$: C, 50.87; H, 7.63; N, 5.81

IR (Neat, λ max cm^{-1}): 2979, 1727, 1706, 1500

^1H NMR (CDCl_3 , δ ppm): 1.4 (s, 9H), 1.7(s, 3H), 3.8 (s, 3H), 5.7 (bs, 1H), 9.6 (s, 1H).

15 ^{13}C NMR (CDCl_3 , δ ppm): 19.23, 27.69, 28.17, 53.33, 67.99, 169.31, 193.83

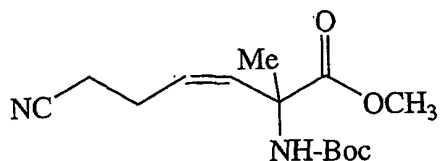
UV, 240 nm, abs 0.072

Mass (M^{+1}) = 232

20

Example 10

Methyl (3Z)-2-[(tert-butoxycarbonyl)amino]-6-cyano-2-methylhex-3-enoate



25 A sample of 3-Cyanopropyltriphenylphosphonium bromide (1.025 g, 0.0025 mol) was taken in dry THF (30 mL) and purged with argon. To this sodium bis(trimethylsilyl)amide (3 mL 1.0M solution in THF, 0.003 mol) was added at 20°C to 25°C and the reaction mixture was stirred at this temperature for 10 min.

when the yellow color change was observed. A solution of the product of **Example 9** (578 mg, 0.0025 mol) in THF (20 mL) was then added and the reaction mixture was stirred under argon for 8 h at 25 °C. It was then concentrated on a rotary evaporator and the residual mass was taken up into EtOAc (100 mL) and washed
 5 with DI water (20 mL). The organic layer was dried over anhydrous MgSO_4 , decolorized with activated charcoal (1.0 g), filtered over Celite and concentrated on a rotary evaporator to give crude dark brown oily reaction product. Column chromatography of this crude product afforded the title product.

10 Elemental analyses Calcd for $\text{C}_{14}\text{H}_{22}\text{N}_2\text{O}_4$: C, 59.56; H, 7.85; N, 9.92. Found for $\text{C}_{14}\text{H}_{22}\text{N}_2\text{O}_4 + 0.2 \text{ H}_2\text{O}$: C, 58.68; H, 8.00; N, 9.87

IR (Neat, λ max cm^{-1}): 2980, 1738, 1703, 1492

^1H NMR (CDCl_3 , δ ppm): 1.42 (s, 9H), 1.67(s, 3H), 2.35 (m, 2H), 2.53 (m, 2H), 3.78 (s, 3H), 5.43-5.48 (m, 1H, $J=11.42$ Hz), 5.5 (bs, 1H), 5.78-5.84 (m, 1H,

15 $J=11.42$ Hz)

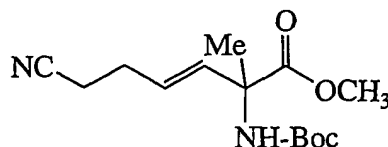
^{13}C NMR (CDCl_3 , δ ppm): 17.01, 23.54, 25.57, 28.25, 53.06, 58.43, 118.95, 128.39, 153.91, 173.82

Mass (M^{+1}) = 283

20

Example 11

Methyl (3E)-2-[(tert-butoxycarbonyl)amino]-6-cyano-2-methylhex-3-enoate



25 In the isolation of the product of **Example 10**, a sample of the title methyl (3E)-2-[(tert-butoxycarbonyl)amino]-6-cyano-2-methylhex-3-enoate was isolated as minor product.

^1H NMR (CDCl_3 , δ ppm): 1.42 (s, 9H), 1.67(s, 3H), 2.35 (m, 2H), 2.53 (m, 2H), 3.78 (s, 3H), 5.43-5.48 (m, 1H, $J=18.5$ Hz), 5.5 (bs, 1H), 5.82-6.0(m, 1H, $J=18.5$ Hz)

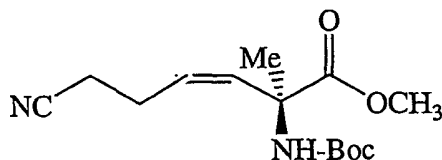
^{13}C NMR (CDCl_3 , δ ppm): 17.01, 23.54, 25.57, 28.25, 53.06, 58.43, 118.95,

5 128.39, 153.91, 173.82

Mass (M^{+1}) = 283

Example 12

10 Methyl (2S,3Z)-2-[(tert-butoxycarbonyl)amino]-6-cyano-2-methylhex-3-enoate

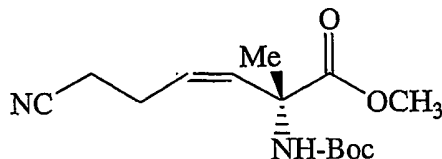


This title compound was isolated by the chiral chromatography of the racemic
15 product of **Example 10**.

Example 13

Methyl (2R,3Z)-2-[(tert-butoxycarbonyl)amino]-6-cyano-2-methylhex-3-enoate

20

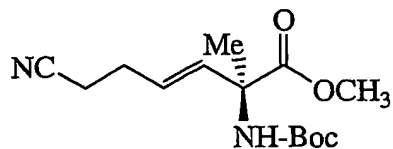


This title compound was isolated by the chiral chromatography of the racemic
product of **Example 10**.

25

Example 14

Methyl (2S,3E)-2-[(tert-butoxycarbonyl)amino]-6-cyano-2-methylhex-3-enoate

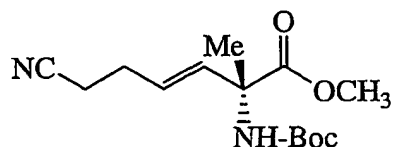


5

This title compound is isolated by the chiral chromatography of the racemic product of Example 11.

10 Example 15

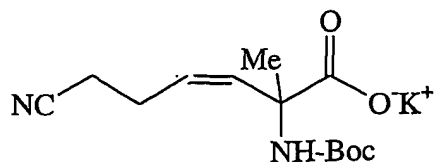
Methyl (2R,3E)-2-[(tert-butoxycarbonyl)amino]-6-cyano-2-methylhex-3-enoate



15 This title compound is isolated by the chiral chromatography of the racemic product of Example 11.

Example 16

20 (3Z)-2-[(tert-butoxycarbonyl)amino]-6-cyano-2-methylhex-3-enoic acid potassium salt



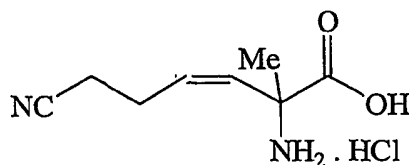
The racemic product of **Example 10** (2.82 g, 0.01 mol) was taken up into DI water (100 mL). To this was added KOH (560 mg, 0.01 mol) and the reaction mixture was stirred for at 50 °C for 3 h. It was then concentrated on rotary evaporator to give the desired title product as a white solid (2.85 g, 93% yield).

5

^1H NMR (D_2O), δ ppm): 1.42 (s, 9H), 1.55 (s, 3H), 2.4 - 2.6 (m, 4H), 5.43 (m, 1H, $J=11.42$ Hz), 5.9 (m, 1H, $J=11.42$)

Example 17

10 (3Z)-2-amino-6-cyano-2-methylhex-3-enoic acid hydrochloride



The racemic product of **Example 16** (2.85 g, 0.0093 mol) was taken up into DI water (80 mL) containing HCl (0.0186 mol). The reaction mixture was stirred at 50 °C for 2 h. and concentrated on rotary evaporator to give the crude product. It was purified using a Gilson chromatographic system to give the desired title product (yield 1.80 g, 92%).

20 Elemental analyses Calcd for $\text{C}_8\text{H}_{12}\text{N}_2\text{O}_2 \cdot \text{HCl}$: C, 46.95; H, 6.40; N, 15.05; Cl, 13.32

Found for $\text{C}_8\text{H}_{12}\text{N}_2\text{O}_2 + 0.4 \text{ H}_2\text{O} + 0.25 \text{ HCl}$: C, 52.01; H, 7.01; N, 15.05; Cl, 4.34

IR (Neat, λ max cm^{-1}): 2900, 2246, 1727, 1631

^1H NMR (D_2O , δ ppm): 1.62 (s, 3H), 2.5 (m, 2H), 2.6 (m, 2H), 5.62 (m, 1H,

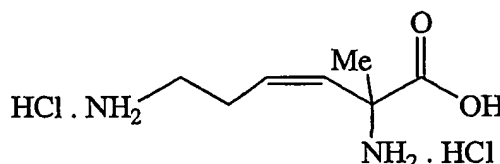
25 $J=11.42$ Hz), 5.8 (m, 1H, $J=11.42$)

^{13}C NMR (D_2O , δ ppm): 18.89, 26.24, 27.28, 61.84, 123.84, 132.33, 136.62, 178.49

Mass (M^{+1}) = 169

Example 18

(3Z)-2,7-diamino-2-methylhept-3-enoic acid dihydrochloride



5

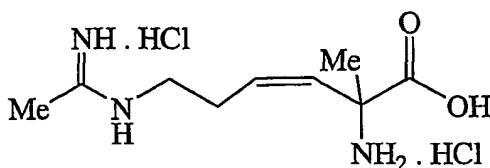
The racemic product of **Example 17** (2.04 g, 0.01 mol) was taken up in MeOH (50 mL). To this solution was added Co(II)Cl₂·6H₂O (4.75 g, 0.02 mol) in one portion with stirring under argon. The reaction mixture turned purple blue. Subsequently, the cautious addition of NaBH₄ (3.76 g, 0.1 mol) in 6 portions over 15 min. at 25 °C turned the reaction mixture black. HCl (4N, 25 mL) was then added carefully and the reaction mixture was stirred until it became light purple in color. It was then concentrated on a rotary evaporator and the residue was subjected to BioRad 'H' form ion exchange resin. Elution with 1% NH₄OH/H₂O gave the desired product solution. It was concentrated (to 50 mL) to drive off NH₃ at < 55 °C on a rotary evaporator and then acidified to pH 4.5 with conc. HCl. It was again concentrated to dryness to afford 2.098 g (85.6%) of the desired title product as an off white solid.

¹H NMR (D₂O, δ ppm): 1.38 (s, 3H), 1.65 (m, 2H), 2.16 (m, 2H), 2.9 (t, 2H), 5.4-5.7 (m, 2H)

Example 19:

(±)-2-Amino-2-methyl-7-[(1-iminoethyl)amino]-3-heptenoic acid, dihydrochloride
or
(3Z)-2-amino-6-(ethanimidoethylamino)-2-methylhex-3-enoic acid dihydrochloride

25



The racemic product of **Example 18** (1.2 g, 0.005 mol) was taken up into DI water (20mL) and treated with 1N NaOH to bring the reaction mixture to pH 8.5. To this mixture under stirring was added ethylacetimidate hydrochloride (600 mg, 0.0049 mol) in 6 portions with simultaneous addition of 1N NaOH to maintain the reaction at 8.5 pH. The stirring was continued for additional 20 min. at 25 °C. 2N HCl was then added to the reaction mixture until the pH was lowered to 2. The mixture was concentrated on rotary evaporator to give the crude product. It was purified using a Gilson chromatographic system to afford the desired title product (830 mg, 30%) as a white hygroscopic solid.

Elemental analyses Calcd for $C_{10}H_{19}N_3O_2 \cdot 2HCl$: C, 39.48; H, 7.62; N, 13.81; Cl, 23.31

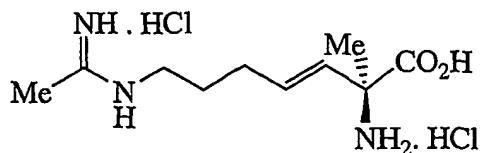
Found for $C_{10}H_{19}N_3O_2 + 1 H_2O + 2 HCl$: C, 39.02; H, 7.51; N, 13.49; Cl, 23.03
 1H NMR (D_2O , δ ppm): 1.62 (s, 3H), 1.65 (m, 2H), 2.1 (s, 3H), 3.15 (t, 2H), 5.45 (m, 1H, $J=11.42$ Hz), 5.75 (m, 1H, $J=11.42$)
 ^{13}C NMR (D_2O , δ ppm): 18.78, 24.34, 25.39, 26.46, 41.89, 58.69, 126.60, 137.83, 165.07, 174.68

Mass (M^{+1}) = 214

Example 20:

(2*S*,3*E*)-2-amino-2-methyl-7-[(1-iminoethyl)amino]-3-heptenoic acid, dihydrochloride

52



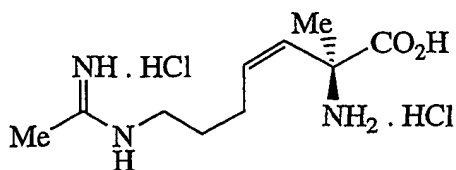
This compound is prepared from the product of **Example 14** following the procedures of **Examples 16, 17, 18, and 19**.

5

Example 21

(2S,3Z)-2-amino-2-methyl-7-[(1-iminoethyl)amino]-3-heptenoic acid, dihydrochloride

10



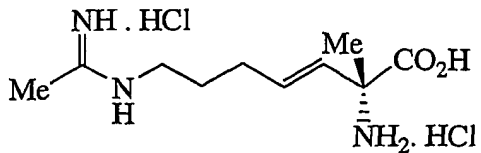
This compound is prepared from the product of **Example 12** following the procedures of **Examples 16, 17, 18, and 19**.

15

Example 22

(2R,3E)-2-amino-2-methyl-7-[(1-iminoethyl)amino]-3-heptenoic acid, dihydrochloride

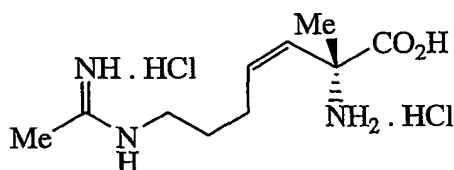
20



The title compound is prepared from the product of **Example 15** following the procedures of **Examples 16, 17, 18, and 19**.

Example 23

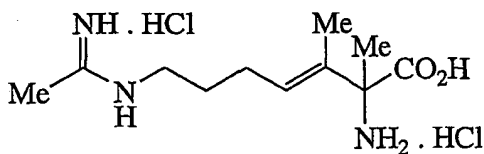
(2R,3Z)-2-amino-2-methyl-7-[(1-iminoethyl)amino]-3-heptenoic acid,
5 dihydrochloride



The title compound is prepared from the product of **Example 13** following the
10 procedures of **Examples 16, 17, 18, and 19.**

Example 24

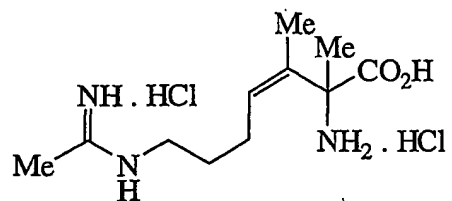
(3E)-2-amino-2,3-dimethyl-7-[(1-iminoethyl)amino]-3-heptenoic acid,
15 dihydrochloride



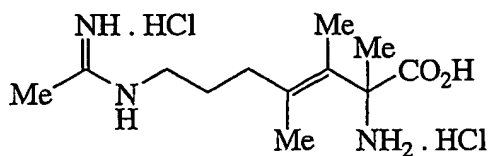
20 Example 25

(3Z)-2-amino-2,3-dimethyl-7-[(1-iminoethyl)amino]-3-heptenoic acid,
dihydrochloride

54

Example 26

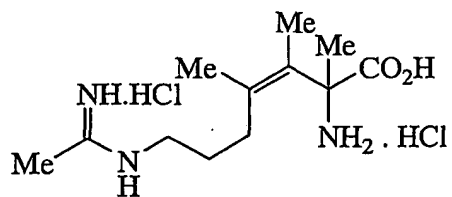
- 5 (3E)-2-amino-2,3,4-trimethyl-7-[(1-iminoethyl)amino]- 3-heptenoic acid,
dihydrochloride



10

Example 27

- (3Z)-2-amino-2,3,4-trimethyl-7-[(1-iminoethyl)amino]- 3-heptenoic acid,
dihydrochloride

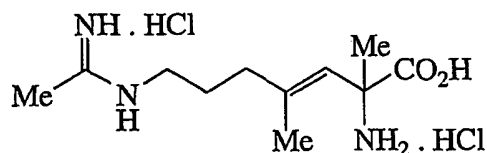


15

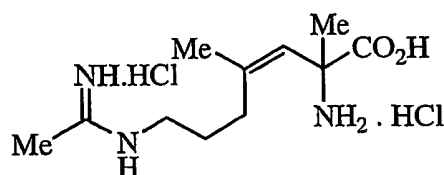
Example 28

- (3E)-2-amino-2,4-dimethyl-7-[(1-iminoethyl)amino]- 3-heptenoic acid,
dihydrochloride

20

Example 29

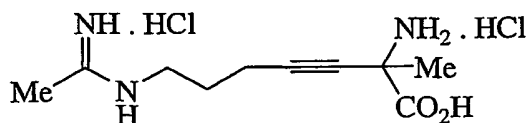
- 5 (3Z)-2-amino-2,4-dimethyl-7-[(1-iminoethyl)amino]-3-heptenoic acid, dihydrochloride



10

Example 30

- 2-amino-2-methyl-7-[(1-iminoethyl)amino]-3-heptynoic acid, dihydrochloride



15

Biological Data

Some or all of the following assays are used to demonstrate the nitric oxide synthase inhibitory activity of the invention's compounds as well as demonstrate the useful pharmacological properties.

20

Citrulline Assay for Nitric Oxide Synthase

Nitric oxide synthase (NOS) activity can be measured by monitoring the conversion of L-[2,3-³H]-arginine to L-[2,3-³H]-citrulline (Bredt and Snyder, Proc.

Natl. Acad. Sci. U.S.A., 87, 682-685, 1990 and Moore et al, J. Med. Chem., 39, 669-672, 1996). Human inducible NOS (hiNOS), human endothelial constitutive NOS (hecNOS) and human neuronal constitutive NOS (hncNOS) are each cloned from RNA extracted from human tissue. The cDNA for human inducible NOS

5 (hiNOS) is isolated from a λ cDNA library made from RNA extracted from a colon sample from a patient with ulcerative colitis. The cDNA for human endothelial constitutive NOS (hecNOS) is isolated from a λ cDNA library made from RNA extracted from human umbilical vein endothelial cells (HUVEC) and the cDNA for human neuronal constitutive NOS (hncNOS) is isolated from a λ cDNA library

10 made from RNA extracted from human cerebellum obtained from a cadaver. The recombinant enzymes are expressed in Sf9 insect cells using a baculovirus vector (Rodi et al, in The Biology of Nitric Oxide, Pt. 4: Enzymology, Biochemistry and Immunology; Moncada, S., Feelisch, M., Busse, R., Higgs, E., Eds.; Portland Press Ltd.: London, 1995; pp 447-450). Enzyme activity is isolated from soluble cell

15 extracts and partially purified by DEAE-Sepharose chromatography. To measure NOS activity, 10 μ L of enzyme is added to 40 μ L of 50 mM Tris (pH 7.6) in the presence or absence of test compounds and the reaction initiated by the addition of 50 μ L of a reaction mixture containing 50mM Tris (pH 7.6), 2.0 mg/mL bovine serum albumin, 2.0 mM DTT, 4.0 mM CaCl_2 , 20 μ M FAD, 100 μ M

20 tetrahydrobiopterin, 0.4 mM NADPH and 60 μ M L-arginine containing 0.9 μ Ci of L-[2,3- ^3H]-arginine. The final concentration of L-arginine in the assay is 30 μ M. For hecNOS or hncNOS, calmodulin is included at a final concentration of 40-100 nM. Following incubation at 37°C for 15 minutes, the reaction is terminated by addition of 400 μ L of a suspension (1 part resin, 3 parts buffer) of Dowex 50W X-8

25 cation exchange resin (sodium form) in a stop buffer containing 10 mM EGTA, 100 mM HEPES, pH 5.5 and 1 mM L-citrulline. After mixing the resin is allowed to settle and L-[2,3- ^3H]-Citrulline formation is determined by counting aliquots of the supernatant with a liquid scintillation counter. IC_{50} values can be determined by testing each compound at several concentrations. Results can be reported as the

30 IC_{50} values of compounds for hiNOS, hecNOS and hncNOS.

In Vivo Assay

Rats can be treated with an intraperitoneal injection of 1-12.5 mg/kg of endotoxin (LPS) to induce systemic expression of inducible nitric oxide synthase, resulting in markedly elevated plasma nitrite/nitrate levels. Compounds are administered orally 0.5-1 hours prior to LPS administration and plasma nitrite/nitrate levels are determined 5 hours following LPS administration. The results can be used to show that the administration of the nitric oxide synthase inhibitors decreases the rise in plasma nitrite/nitrate levels, a reliable indicator of the production of nitric oxide induced by endotoxin. ED₅₀ values (mg/kg) for inhibition of the LPS-induced increase in plasma nitrite/nitrate levels can be determined.

Raw Cell Nitrite Assay

RAW 264.7 cells can be plated to confluency on a 96-well tissue culture plate grown overnight (17h) in the presence of LPS to induce NOS. A row of 3-6 wells can be left untreated and serve as controls for subtraction of nonspecific background. The media can be removed from each well and the cells washed twice with Krebs-Ringers-Hepes (25 mM, pH 7.4) with 2 mg/ml glucose. The cells are then placed on ice and incubated with 50 μ L of buffer containing L-arginine (30 μ M) +/- inhibitors for 1h. The assay can be initiated by warming the plate to 37° C in a water bath for 1h. Production of nitrite by intracellular iNOS will be linear with time. To terminate the cellular assay, the plate of cells can be placed on ice and the nitrite-containing buffer removed and analyzed for nitrite using a previously published fluorescent determination for nitrite (T. P. Misko et al, Analytical Biochemistry, 214, 11-16, 1993).

Human cartilage explant assay

Bone pieces are rinsed twice with Dulbecco's Phosphate Buffered Saline (GibcoBRL) and once with Dulbecco's Modified Eagles Medium (GibcoBRL) and

placed into a petri dish with phenol red free Minimum Essential Medium (MEM) (GibcoBRL). Cartilage is cut into small explants of approximately 15-45 mg in weight and one or two explants per well are placed into either 96 or 48 well culture plates with 200-500 μ L of culture media per well. The culture media is either a custom modification of Minimum Essential Medium(Eagle) with Earle's salts (GibcoBRL) prepared without L-Arginine, without L-Glutamine and without phenol red or a custom modification of serumless Neuman and Tytell (GibcoBRL) medium prepared without L-arginine, without insulin, without ascorbic acid, without L-glutamine and without phenol red. Both are supplemented before use with 100 μ M L-Arginine (Sigma), 2 mM L-glutamine, 1X HL-1 supplement (BioWhittaker), 50 mg/ml ascorbic acid (Sigma) and 150 pg/ml recombinant human IL-1 β (RD Systems) to induce nitric oxide synthase. Compounds are then added in 10 μ L aliquots and the explants incubated at 37° C with 5% CO₂ for 18-24 hours. The day old supernatant is then discarded and replaced with fresh culture media containing recombinant human IL-1 β and compound and incubated for another 20-24 hours. This supernatant is analyzed for nitrite with a fluorometric assay (Misko et al, Anal. Biochem., 214, 11-16, 1993). All samples are done in quadruplicate. Unstimulated controls are cultured in media in the absence of recombinant human IL-1 β . IC₅₀ values are determined from plotting the percent inhibition of nitrite production at six different concentrations of inhibitor.

Assay for Time Dependent Inhibition

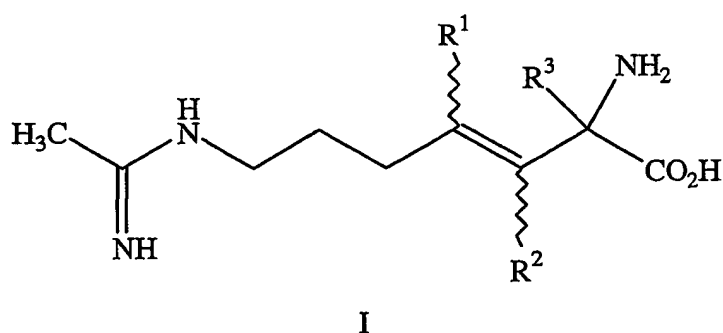
Compounds are evaluated for time dependent inhibition of human NOS isoforms by preincubation of the compound with the enzyme at 37° C in the presence of the citrulline enzyme assay components, minus L-arginine, for times ranging from 0-60 minutes. Aliquots (10 μ L) are removed at 0, 10, 21 and 60 minutes and immediately added to a citrulline assay enzyme reaction mixture containing L-[2,3-³H]-arginine and a final L-arginine concentration of 30 μ M in a final volume of 100 μ L. The reaction is allowed to proceed for 15 minutes at 37° C and terminated by addition of a suspension of Dowex 50W X-8 cation exchange

resin as described above for the citrulline NOS assay. The % inhibition of NOS activity by an inhibitor is taken as the per cent inhibition in activity compared to control enzyme preincubated for the same time in the absence of inhibitor. Time-dependent inhibition can be demonstrated as an increase in inhibition with

5 increasing preincubation time.

What is Claimed:

- 5 1. A compound of Formula I:



- 10 or a pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from the group consisting of hydrogen, halo, and C_1 - C_5 alkyl, said C_1 - C_5 alkyl optionally substituted by halo or alkoxy, said alkoxy optionally substituted by one or more halo;

- 15 R^2 is selected from the group consisting of hydrogen, halo, and C_1 - C_5 alkyl, said C_1 - C_5 alkyl optionally substituted by halo or alkoxy, said alkoxy optionally substituted by one or more halo; and

R^3 is C_1 - C_5 alkyl, said C_1 - C_5 alkyl optionally substituted by halo or alkoxy, said alkoxy optionally substituted by one or more halo.

20

2. The compound of claim 1 wherein the compound is the Z isomer.

3. The compound of claim 2 wherein:

R^1 is selected from the group consisting of hydrogen, halo, and C_1 - C_5 alkyl, said C_1 - C_5 alkyl optionally substituted by halo or alkoxy, said alkoxy optionally substituted by one or more halo;

25

R² is selected from the group consisting of hydrogen, halo and C₁-C₅ alkyl, said C₁-C₅ alkyl optionally substituted by halo or alkoxy, said alkoxy optionally substituted by one or more halo; and
R³ is C₁-C₅ alkyl, said C₁-C₅ alkyl optionally substituted by halo or alkoxy.

5

4. The compound of claim 3 wherein:

R¹ is selected from the group consisting of hydrogen, halo, and C₁-C₃ alkyl;
R² is selected from the group consisting of hydrogen, halo and C₁-C₃ alkyl;
and

10 R³ is C₁-C₅ alkyl, said C₁-C₅ alkyl optionally substituted by fluorine or alkoxy.

5. The compound of claim 3 wherein:

R¹ is selected from the group consisting of hydrogen, halo, and C₁-C₃ alkyl;
said C₁-C₅ alkyl optionally substituted by halo or alkoxy, said alkoxy
optionally substituted by one or more halo;

15

R² is selected from the group consisting of hydrogen, halo and C₁-C₅ alkyl;
and

R³ is C₁-C₅ alkyl, said C₁-C₅ alkyl optionally substituted by halo or alkoxy.

20

6. The compound of claim 3 wherein:

R¹ is selected from the group consisting of hydrogen, halo, and C₁-C₃ alkyl;
R² is selected from the group consisting of hydrogen, halo and C₁-C₃ alkyl;
and

25 R³ is C₁-C₃ alkyl optionally substituted by fluorine.

7. The compound of claim 3 wherein:

R¹ is selected from the group consisting of hydrogen, halo, and C₁-C₃ alkyl;
R² is selected from the group consisting of hydrogen, halo and C₁-C₃ alkyl;
and

30

R^3 is C_1-C_3 alkyl.

8. The compound of claim 3 wherein:

R^1 is hydrogen;

5 R^2 is selected from the group consisting of hydrogen, halo and C_1-C_3 alkyl;

and

R^3 is C_1-C_3 alkyl.

9. The compound of claim 8 wherein:

10 R^1 is hydrogen;

R^2 is selected from the group consisting of hydrogen and halo; and

R^3 is C_1-C_3 alkyl.

10. The compound of claim 9 wherein:

15 R^1 is hydrogen;

R^2 is selected from the group consisting of hydrogen and fluorine; and

R^3 is C_1-C_3 alkyl.

11. The compound of claim 10 wherein:

20 R^1 is hydrogen;

R^2 is selected from the group consisting of hydrogen and fluorine; and

R^3 is methyl.

12. The compound of claim 11 wherein:

25 R^1 is hydrogen;

R^2 is hydrogen; and

R^3 is methyl.

13. The compound of claim 11 wherein:

30 R^1 is hydrogen;

R^2 is fluorine; and

R^3 is methyl.

14. The compound of claim 3 wherein:

5 R^1 is halo;

R^2 is selected from the group consisting of hydrogen, halo and C_1 - C_3 alkyl;

and

R^3 is C_1 - C_3 alkyl.

10 15. The compound of claim 14 wherein:

R^1 is halo;

R^2 is halo; and

R^3 is C_1 - C_3 alkyl.

15 16. The compound of claim 15 wherein:

R^1 is fluorine;

R^2 is fluorine; and

R^3 is methyl.

20 17. The compound of claim 14 wherein:

R^1 is fluorine;

R^2 is selected from the group consisting of hydrogen and C_1 - C_3 alkyl; and

R^3 is methyl.

25 18. The compound of claim 17 wherein:

R^1 is fluorine;

R^2 is hydrogen; and

R^3 is methyl.

30 19. The compound of claim 3 wherein:

R¹ is methyl;
R² is hydrogen; and
R³ is methyl.

5 20. The compound of claim 3 wherein:

R¹ is hydrogen;
R² is methyl; and
R³ is methyl.

10 21. The compound of claim 3 wherein:

R¹ is methyl;
R² is methyl; and
R³ is methyl.

15 22. The compound of claim 2 wherein:

R¹ is selected from the group consisting of hydrogen, halo and C₁-C₅ alkyl,
said C₁-C₅ alkyl optionally substituted by alkoxy or one or more fluorine;
R² is selected from the group consisting of hydrogen, halo and C₁-C₅ alkyl,
said C₁-C₅ alkyl optionally substituted by alkoxy or one or more fluorine;
20 and
R³ is methyl optionally substituted by one or more alkoxy or halo.

23. The compound of claim 22 wherein:

R¹ is selected from the group consisting of hydrogen and fluorine;
25 R² is C₁-C₃ alkyl substituted by one or more halo; and
R³ is methyl.

24. The compound of claim 23 wherein:

R¹ is hydrogen;
30 R² is CH₂F; and
R³ is methyl.

25. The compound of claim 22 wherein:

R¹ is CH₂F;

R² is hydrogen; and

5 R³ is methyl.

26. The compound of claim 22 wherein:

R¹ is hydrogen;

R² is hydrogen; and

10 R³ is CH₂F.

27. The compound of claim 22 wherein:

R¹ is hydrogen;

R² is methoxymethyl; and

15 R³ is methyl.

28. The compound of claim 22 wherein:

R¹ is methoxymethyl;

R² is hydrogen; and

20 R³ is methyl.

29. The compound of claim 22 wherein:

R¹ is hydrogen;

R² is hydrogen; and

25 R³ is methoxymethyl.

30. The compound of claim 1 wherein the compound is the E isomer.

31. The compound of claim 30 wherein:

R¹ is selected from the group consisting of hydrogen, halo, and C₁-C₅ alkyl, said C₁-C₅ alkyl optionally substituted by halo or alkoxy, said alkoxy optionally substituted by one or more halo;

5 R² is selected from the group consisting of hydrogen, halo and C₁-C₅ alkyl, said C₁-C₅ alkyl optionally substituted by halo or alkoxy, said alkoxy optionally substituted by one or more halo; and

R³ is C₁-C₅ alkyl, said C₁-C₅ alkyl optionally substituted by one or more halo or alkoxy.

10 32. The compound of claim 31 wherein:

R¹ is selected from the group consisting of hydrogen, halo, and C₁-C₃ alkyl; said C₁-C₅ alkyl optionally substituted by halo or alkoxy, said alkoxy optionally substituted by one or more halo;

15 R² is selected from the group consisting of hydrogen, halo and C₁-C₅ alkyl; and

R³ is C₁-C₅ alkyl, said C₁-C₅ alkyl optionally substituted by halo or alkoxy.

33. The compound of claim 31 wherein:

R¹ is selected from the group consisting of hydrogen, halo, and C₁-C₃ alkyl;

20 R² is selected from the group consisting of hydrogen, halo and C₁-C₃ alkyl; and

R³ is C₁-C₃ alkyl optionally substituted by fluorine.

34. The compound of claim 31 wherein:

25 R¹ is selected from the group consisting of hydrogen, halo, and C₁-C₃ alkyl;

R² is selected from the group consisting of hydrogen, halo and C₁-C₃ alkyl; and

R³ is C₁-C₅ alkyl, said C₁-C₅ alkyl optionally substituted by fluorine or alkoxy.

30

35. The compound of claim 31 wherein:

R^1 is selected from the group consisting of hydrogen, halo, and C_1 - C_3 alkyl;
 R^2 is selected from the group consisting of hydrogen, halo and C_1 - C_3 alkyl;
and
 R^3 is C_1 - C_3 alkyl.

5

36. The compound of claim 31 wherein:

R^1 is hydrogen;

R^2 is selected from the group consisting of hydrogen, halo and C_1 - C_3 alkyl;

and

10

R^3 is C_1 - C_3 alkyl.

37. The compound of claim 36 wherein:

R^1 is hydrogen;

R^2 is selected from the group consisting of hydrogen and halo; and

15

R^3 is C_1 - C_3 alkyl.

38. The compound of claim 37 wherein:

R^1 is hydrogen;

R^2 is selected from the group consisting of hydrogen and fluorine; and

20

R^3 is C_1 - C_3 alkyl.

39. The compound of claim 38 wherein:

R^1 is hydrogen;

R^2 is selected from the group consisting of hydrogen and fluorine; and

25

R^3 is methyl.

40. The compound of claim 39 wherein:

R^1 is hydrogen;

R^2 is hydrogen; and

30

R^3 is methyl.

41. The compound of claim 39 wherein:
R¹ is hydrogen;
R² is fluorine; and
5 R³ is methyl.
42. The compound of claim 31 wherein:
R¹ is halo;
R² is selected from the group consisting of hydrogen, halo and C₁-C₃ alkyl;
10 and
R³ is C₁-C₃ alkyl.
43. The compound of claim 42 wherein:
R¹ is halo;
15 R² is halo; and
R³ is C₁-C₃ alkyl.
44. The compound of claim 39 wherein:
R¹ is fluorine;
20 R² is fluorine; and
R³ is methyl.
45. The compound of claim 42 wherein:
R¹ is fluorine;
25 R² is selected from the group consisting of hydrogen and C₁-C₃ alkyl; and
R³ is methyl.
46. The compound of claim 45 wherein:
R¹ is fluorine;
30 R² is hydrogen; and

R³ is methyl.

47. The compound of claim 31 wherein:

R¹ is methyl;

5 R² is hydrogen; and

R³ is methyl.

48. The compound of claim 31 wherein:

R¹ is hydrogen;

10 R² is methyl; and

R³ is methyl.

49. The compound of claim 31 wherein:

R¹ is methyl;

15 R² is methyl; and

R³ is methyl.

50. The compound of claim 30 wherein:

20 R¹ is selected from the group consisting of hydrogen, halo and C₁-C₅ alkyl,
said C₁-C₅ alkyl optionally substituted by alkoxy or one or more fluorine;

R² is selected from the group consisting of hydrogen, halo and C₁-C₅ alkyl,
said C₁-C₅ alkyl optionally substituted by alkoxy or one or more fluorine;
and

25 R³ is methyl optionally substituted by alkoxy or one or more halo.

51. The compound of claim 50 wherein:

R¹ is selected from the group consisting of hydrogen and fluorine;

R² is C₁-C₃ alkyl substituted by one or more halo; and

30 R³ is methyl.

52. The compound of claim 51 wherein:

R^1 is hydrogen;
 R^2 is CH_2F ; and
 R^3 is methyl.

5 53. The compound of claim 50 wherein:

R^1 is CH_2F ;
 R^2 is hydrogen; and
 R^3 is methyl.

10 54. The compound of claim 50 wherein:

R^1 is hydrogen;
 R^2 is hydrogen; and
 R^3 is CH_2F .

15 55. The compound of claim 50 wherein:

R^1 is hydrogen;
 R^2 is methoxymethyl; and
 R^3 is methyl.

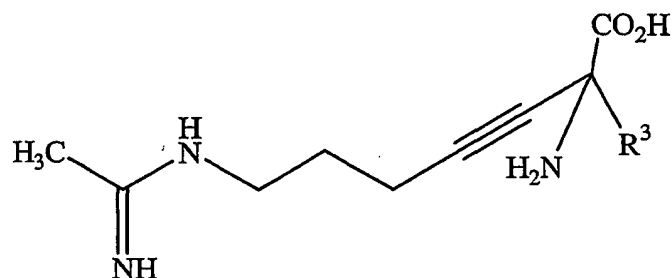
20 56. The compound of claim 50 wherein:

R^1 is methoxymethyl;
 R^2 is hydrogen; and
 R^3 is methyl.

25 57. The compound of claim 50 wherein:

R^1 is hydrogen;
 R^2 is hydrogen; and
 R^3 is methoxymethyl.

30 58. A compound of Formula II



II

5 or a pharmaceutically acceptable salt thereof, wherein:

R³ is C₁-C₅ alkyl, said C₁-C₅ alkyl optionally substituted by halo or alkoxy, said alkoxy optionally substituted by one or more halo.

59. The compound of claim 58 wherein:

10 R³ is C₁-C₅ alkyl substituted by one or more halo.

60. The compound of claim 59 wherein:

R³ is C₁-C₅ alkyl substituted by one or more fluorine.

15 61. The compound of claim 59 wherein:

R³ is methyl substituted by one or more halo.

62. The compound of claim 61 wherein:

R³ is methyl substituted by one or more fluorine.

20 63. The compound of claim 61 wherein:

R³ is CH₂F.

64. The compound recited in claim 59 wherein:

25 R³ is C₁-C₅ alkyl substituted by alkoxy.

65. The compound of claim 64 wherein:

R^3 is methoxy methyl.

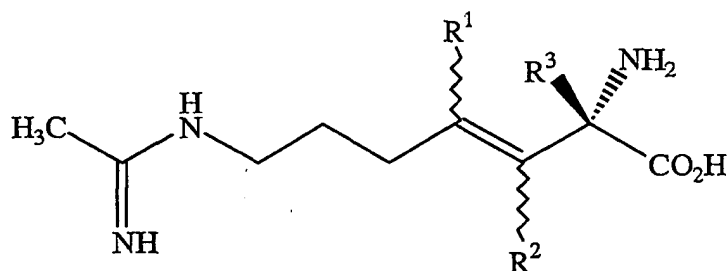
66. The compound of claim 59 wherein:

5 R^3 is C_1 - C_5 alkyl.

67. The compound of claim 65 wherein:

R^3 is methyl.

10 68. A compound of Formula III



15 III

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from the group consisting of hydrogen, halo, and C_1 - C_5 alkyl, said C_1 - C_5 alkyl optionally substituted by halo or alkoxy, said alkoxy optionally substituted by one or more halo;

20 R^2 is selected from the group consisting of hydrogen, halo, and C_1 - C_5 alkyl, said C_1 - C_5 alkyl optionally substituted by halo or alkoxy, said alkoxy optionally substituted by one or more halo; and

R^3 is C_1 - C_5 alkyl, said C_1 - C_5 alkyl optionally substituted by halo or alkoxy, said alkoxy optionally substituted by one or more halo.

25

69. The compound of claim 68 wherein the compound is the Z isomer.

70. The compound of claim 69 wherein:

R¹ is selected from the group consisting of hydrogen, halo, and C₁-C₅ alkyl, said C₁-C₅ alkyl optionally substituted by halo or alkoxy, said alkoxy optionally substituted by one or more halo;

R² is selected from the group consisting of hydrogen, halo and C₁-C₅ alkyl, said C₁-C₅ alkyl optionally substituted by halo or alkoxy, said alkoxy optionally substituted by one or more halo; and

R³ is C₁-C₅ alkyl, said C₁-C₅ alkyl optionally substituted by one or more halo or alkoxy.

71. The compound of claim 69 wherein:

R¹ is selected from the group consisting of hydrogen, halo, and C₁-C₃ alkyl; said C₁-C₅ alkyl optionally substituted by halo or alkoxy, said alkoxy optionally substituted by one or more halo;

R² is selected from the group consisting of hydrogen, halo and C₁-C₅ alkyl; and

R³ is C₁-C₅ alkyl, said C₁-C₅ alkyl optionally substituted by halo or alkoxy

72. The compound of claim 69 wherein:

R¹ is selected from the group consisting of hydrogen, halo, and C₁-C₃ alkyl;

R² is selected from the group consisting of hydrogen, halo and C₁-C₃ alkyl; and

R³ is C₁-C₃ alkyl optionally substituted by fluorine.

73. The compound of claim 70 wherein:

R¹ is selected from the group consisting of hydrogen, halo, and C₁-C₃ alkyl;

R² is selected from the group consisting of hydrogen, halo and C₁-C₃ alkyl; and

R^3 is C_1 - C_5 alkyl, said C_1 - C_5 alkyl optionally substituted by fluorine or alkoxy.

74. The compound of claim 70 wherein:

5 R^1 is selected from the group consisting of hydrogen, halo, and C_1 - C_3 alkyl;
 R^2 is selected from the group consisting of hydrogen, halo and C_1 - C_3 alkyl;
and
 R^3 is C_1 - C_3 alkyl.

10 75. The compound of claim 70 wherein:

R^1 is hydrogen;
 R^2 is selected from the group consisting of hydrogen, halo and C_1 - C_3 alkyl;
and
 R^3 is C_1 - C_3 alkyl.

15 76. The compound of claim 75 wherein:

R^1 is hydrogen;
 R^2 is selected from the group consisting of hydrogen and halo; and
 R^3 is C_1 - C_3 alkyl.

20 77. The compound of claim 76 wherein:

R^1 is hydrogen;
 R^2 is selected from the group consisting of hydrogen and fluorine; and
 R^3 is C_1 - C_3 alkyl.

25 78. The compound of claim 77 wherein:

R^1 is hydrogen;
 R^2 is selected from the group consisting of hydrogen and fluorine; and
 R^3 is methyl.

79. The compound of claim 78 wherein:

R¹ is hydrogen;

R² is hydrogen; and

R³ is methyl.

5

80. The compound of claim 78 wherein:

R¹ is hydrogen;

R² is fluorine; and

R³ is methyl.

10

81. The compound of claim 70 wherein:

R¹ is halo;

R² is selected from the group consisting of hydrogen, halo and C₁-C₃ alkyl;

and

15

R³ is C₁-C₃ alkyl.

82. The compound of claim 81 wherein:

R¹ is halo;

R² is halo; and

20

R³ is C₁-C₃ alkyl.

83. The compound of claim 82 wherein:

R¹ is fluorine;

R² is fluorine; and

25

R³ is methyl.

84. The compound of claim 81 wherein:

R¹ is fluorine;

R² is selected from the group consisting of hydrogen and C₁-C₃ alkyl; and

30

R³ is methyl.

85. The compound of claim 84 wherein:
R¹ is fluorine;
R² is hydrogen; and
5 R³ is methyl.
86. The compound of claim 70 wherein:
R¹ is methyl;
R² is hydrogen; and
10 R³ is methyl.
87. The compound of claim 70 wherein:
R¹ is hydrogen;
R² is methyl; and
15 R³ is methyl.
88. The compound of claim 70 wherein:
R¹ is methyl;
R² is methyl; and
20 R³ is methyl.
89. The compound of claim 69 wherein:
R¹ is selected from the group consisting of hydrogen, halo and C₁-C₅ alkyl,
said C₁-C₅ alkyl optionally substituted by alkoxy or one or more fluorine;
25 R² is selected from the group consisting of hydrogen, halo and C₁-C₅ alkyl,
said C₁-C₅ alkyl optionally substituted by alkoxy or one or more fluorine;
and
R³ is methyl optionally substituted by one or more alkoxy or halo.
90. The compound of claim 89 wherein:
30 R¹ is selected from the group consisting of hydrogen and fluorine;

R^2 is C_1 - C_3 alkyl substituted by one or more halo; and
 R^3 is methyl.

5 91. The compound of claim 90 wherein:
 R^1 is hydrogen;
 R^2 is CH_2F ; and
 R^3 is methyl.

10 92. The compound of claim 89 wherein:
 R^1 is CH_2F ;
 R^2 is hydrogen; and
 R^3 is methyl.

15 93. The compound of claim 89 wherein:
 R^1 is hydrogen;
 R^2 is hydrogen; and
 R^3 is CH_2F .

20 94. The compound of claim 89 wherein:
 R^1 is hydrogen;
 R^2 is methoxymethyl; and
 R^3 is methyl.

25 95. The compound of claim 89 wherein:
 R^1 is methoxymethyl;
 R^2 is hydrogen; and
 R^3 is methyl.

30 96. The compound of claim 89 wherein:
 R^1 is hydrogen;

R^2 is hydrogen; and
 R^3 is methoxymethyl.

97. The compound of claim 68 wherein the compound is the E isomer.

5

98. The compound of claim 97 wherein:

R^1 is selected from the group consisting of hydrogen, halo, and C_1 - C_5 alkyl, said C_1 - C_5 alkyl optionally substituted by halo or alkoxy, said alkoxy optionally substituted by one or more halo;

10 R^2 is selected from the group consisting of hydrogen, halo and C_1 - C_5 alkyl, said C_1 - C_5 alkyl optionally substituted by halo or alkoxy, said alkoxy optionally substituted by one or more halo; and

R^3 is C_1 - C_5 alkyl, said C_1 - C_5 alkyl optionally substituted by one or more halo or alkoxy.

15

99. The compound of claim 98 wherein:

R^1 is selected from the group consisting of hydrogen, halo, and C_1 - C_3 alkyl; said C_1 - C_5 alkyl optionally substituted by halo or alkoxy, said alkoxy optionally substituted by one or more halo;

20 R^2 is selected from the group consisting of hydrogen, halo and C_1 - C_5 alkyl; and

R^3 is C_1 - C_5 alkyl, said C_1 - C_5 alkyl optionally substituted by halo or alkoxy

100. The compound of claim 98 wherein:

25 R^1 is selected from the group consisting of hydrogen, halo, and C_1 - C_3 alkyl;
 R^2 is selected from the group consisting of hydrogen, halo and C_1 - C_3 alkyl; and

R^3 is C_1 - C_3 alkyl optionally substituted by fluorine.

30

101. The compound of claim 98 wherein:

R^1 is selected from the group consisting of hydrogen, halo, and C_1 - C_3 alkyl;
 R^2 is selected from the group consisting of hydrogen, halo and C_1 - C_3 alkyl;
and
 R^3 is C_1 - C_5 alkyl, said C_1 - C_5 alkyl optionally substituted by one or more
5 fluorine or alkoxy.

102. The compound of claim 98 wherein:

R^1 is selected from the group consisting of hydrogen, halo, and C_1 - C_3 alkyl;
 R^2 is selected from the group consisting of hydrogen, halo and C_1 - C_3 alkyl;
10 and
 R^3 is C_1 - C_3 alkyl.

103. The compound of claim 98 wherein:

R^1 is hydrogen;
15 R^2 is selected from the group consisting of hydrogen, halo and C_1 - C_3 alkyl;
and
 R^3 is C_1 - C_3 alkyl.

104. The compound of claim 103 wherein:

20 R^1 is hydrogen;
 R^2 is selected from the group consisting of hydrogen and halo; and
 R^3 is C_1 - C_3 alkyl.

105. The compound of claim 104 wherein:

25 R^1 is hydrogen;
 R^2 is selected from the group consisting of hydrogen and fluorine; and
 R^3 is C_1 - C_3 alkyl.

106. The compound of claim 105 wherein:

30 R^1 is hydrogen;

R^2 is selected from the group consisting of hydrogen and fluorine; and
 R^3 is methyl.

5 107. The compound of claim 106 wherein:

R^1 is hydrogen;
 R^2 is hydrogen; and
 R^3 is methyl.

10 108. The compound of claim 106 wherein:

R^1 is hydrogen;
 R^2 is fluorine; and
 R^3 is methyl.

15 109. The compound of claim 98 wherein:

R^1 is halo;
 R^2 is selected from the group consisting of hydrogen, halo and C_1 - C_3 alkyl;
and
 R^3 is C_1 - C_3 alkyl.

20 110. The compound of claim 109 wherein:

R^1 is halo;
 R^2 is halo; and
 R^3 is C_1 - C_3 alkyl.

25 111. The compound of claim 110 wherein:

R^1 is fluorine;
 R^2 is fluorine; and
 R^3 is methyl.

30 112. The compound of claim 109 wherein:

R¹ is fluorine;

R² is selected from the group consisting of hydrogen and C₁-C₃ alkyl; and

R³ is methyl.

5 113. The compound of claim 112 wherein:

R¹ is fluorine;

R² is hydrogen; and

R³ is methyl.

10 114. The compound of claim 98 wherein:

R¹ is methyl;

R² is hydrogen; and

R³ is methyl.

15 115. The compound of claim 98 wherein:

R¹ is hydrogen;

R² is methyl; and

R³ is methyl.

20 116. The compound of claim 98 wherein:

R¹ is methyl;

R² is methyl; and

R³ is methyl.

25 117. The compound of claim 97 wherein:

R¹ is selected from the group consisting of hydrogen, halo and C₁-C₅ alkyl,
said C₁-C₅ alkyl optionally substituted by alkoxy or one or more fluorine;

R² is selected from the group consisting of hydrogen, halo and C₁-C₅ alkyl,
said C₁-C₅ alkyl optionally substituted by alkoxy or one or more fluorine;

30 and

R³ is methyl optionally substituted by one or more alkoxy or halo.

118. The compound of claim 117 wherein:
R¹ is selected from the group consisting of hydrogen and fluorine;
R² is C₁-C₃ alkyl substituted by one or more halo; and
5 R³ is methyl.

119. The compound of claim 118 wherein:
R¹ is hydrogen;
R² is CH₂F; and
10 R³ is methyl.

120. The compound of claim 117 wherein:
R¹ is CH₂F;
R² is hydrogen; and
15 R³ is methyl.

121. The compound of claim 117 wherein:
R¹ is hydrogen;
R² is hydrogen; and
20 R³ is CH₂F.

122. The compound of claim 117 wherein:
R¹ is hydrogen;
R² is methoxymethyl; and
25 R³ is methyl.

123. The compound of claim 117 wherein:
R¹ is methoxymethyl;
R² is hydrogen; and
30 R³ is methyl.

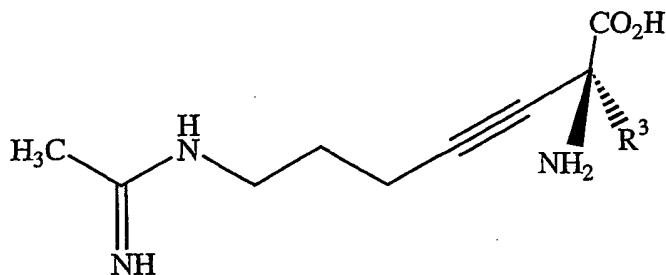
124. The compound of claim 117 wherein:

R^1 is hydrogen;

R^2 is hydrogen; and

5 R^3 is methoxymethyl.

125. A compound of Formula IV



10

IV

or a pharmaceutically acceptable salt thereof, wherein:

R^3 is C_1 - C_5 alkyl, said C_1 - C_5 alkyl optionally substituted by halo or alkoxy,
said alkoxy optionally substituted by one or more halo.

15

126. The compound of claim 125 wherein:

R^3 is C_1 - C_5 alkyl substituted by one or more halo.

127. The compound of claim 126 wherein:

20 R^3 is C_1 - C_5 alkyl substituted by one or more fluorine.

128. The compound of claim 126 wherein:

R^3 is methyl substituted by one or more halo.

25 129. The compound of claim 128 wherein:

R^3 is methyl substituted by one or more fluorine.

130. The compound of claim 128 wherein:

R^3 is CH_2F .

5 131. The compound recited in claim 126 wherein:

R^3 is C_1 - C_5 alkyl substituted by alkoxy.

132. The compound of claim 131 wherein:

R^3 is methoxy methyl.

10

133. The compound of claim 126 wherein:

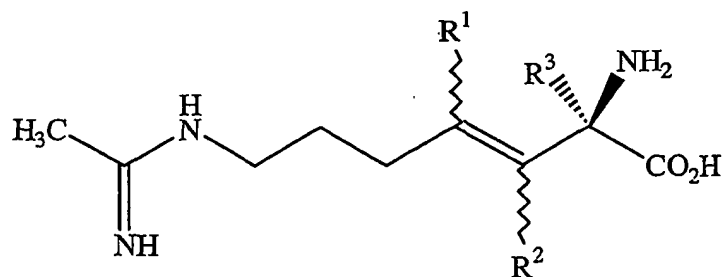
R^3 is C_1 - C_5 alkyl.

134. The compound of claim 132 wherein:

15

R^3 is methyl.

135. A compound of Formula V



20

V

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from the group consisting of hydrogen, halo, and C_1 - C_5 alkyl,

said C_1 - C_5 alkyl optionally substituted by halo or alkoxy, said alkoxy

25

optionally substituted by one or more halo;

R^2 is selected from the group consisting of hydrogen, halo, and C_1 - C_5 alkyl, said C_1 - C_5 alkyl optionally substituted by halo or alkoxy, said alkoxy optionally substituted by one or more halo; and
 R^3 is C_1 - C_5 alkyl, said C_1 - C_5 alkyl optionally substituted by halo or alkoxy,
5 said alkoxy optionally substituted by one or more halo.

136. The compound of claim 135 wherein the compound is the Z isomer.

137. The compound of claim 136 wherein:

10 R^1 is selected from the group consisting of hydrogen, halo, and C_1 - C_5 alkyl, said C_1 - C_5 alkyl optionally substituted by halo or alkoxy, said alkoxy optionally substituted by one or more halo;
 R^2 is selected from the group consisting of hydrogen, halo and C_1 - C_5 alkyl, said C_1 - C_5 alkyl optionally substituted by halo or alkoxy, said alkoxy
15 optionally substituted by one or more halo; and
 R^3 is C_1 - C_5 alkyl, said C_1 - C_5 alkyl optionally substituted by halo or alkoxy.

138. The compound of claim 137 wherein:

R^1 is selected from the group consisting of hydrogen, halo, and C_1 - C_3 alkyl;
20 said C_1 - C_5 alkyl optionally substituted by halo or alkoxy, said alkoxy optionally substituted by one or more halo;
 R^2 is selected from the group consisting of hydrogen, halo and C_1 - C_5 alkyl;
and
 R^3 is C_1 - C_5 alkyl, said C_1 - C_5 alkyl optionally substituted by halo or alkoxy

25

139. The compound of claim 137 wherein:

R^1 is selected from the group consisting of hydrogen, halo, and C_1 - C_3 alkyl;
 R^2 is selected from the group consisting of hydrogen, halo and C_1 - C_3 alkyl;
and
30 R^3 is C_1 - C_3 alkyl optionally substituted by fluorine.

140. The compound of claim 136 wherein:

R^1 is selected from the group consisting of hydrogen, halo, and C_1-C_3 alkyl;

R^2 is selected from the group consisting of hydrogen, halo and C_1-C_3 alkyl;

5 and

R^3 is C_1-C_5 alkyl, said C_1-C_5 alkyl optionally substituted by fluorine or alkoxy.

141. The compound of claim 137 wherein:

10 R^1 is selected from the group consisting of hydrogen, halo, and C_1-C_3 alkyl;

R^2 is selected from the group consisting of hydrogen, halo and C_1-C_3 alkyl;

and

R^3 is C_1-C_3 alkyl.

15 142. The compound of claim 137 wherein:

R^1 is hydrogen;

R^2 is selected from the group consisting of hydrogen, halo and C_1-C_3 alkyl;

and

R^3 is C_1-C_3 alkyl.

20

143. The compound of claim 142 wherein:

R^1 is hydrogen;

R^2 is selected from the group consisting of hydrogen and halo; and

R^3 is C_1-C_3 alkyl.

25

144. The compound of claim 143 wherein:

R^1 is hydrogen;

R^2 is selected from the group consisting of hydrogen and fluorine; and

R^3 is C_1-C_3 alkyl.

30

145. The compound of claim 144 wherein:

R¹ is hydrogen;

R² is selected from the group consisting of hydrogen and fluorine; and

R³ is methyl.

5

146. The compound of claim 145 wherein:

R¹ is hydrogen;

R² is hydrogen; and

R³ is methyl.

10

147. The compound of claim 145 wherein:

R¹ is hydrogen;

R² is fluorine; and

R³ is methyl.

15

148. The compound of claim 137 wherein:

R¹ is halo;

R² is selected from the group consisting of hydrogen, halo and C₁-C₃ alkyl;

and

20

R³ is C₁-C₃ alkyl.

149. The compound of claim 148 wherein:

R¹ is halo;

R² is halo; and

25

R³ is C₁-C₃ alkyl.

150. The compound of claim 149 wherein:

R¹ is fluorine;

R² is fluorine; and

30

R³ is methyl.

151. The compound of claim 148 wherein:
R¹ is fluorine;
R² is selected from the group consisting of hydrogen and C₁-C₃ alkyl; and
5 R³ is methyl.

152. The compound of claim 151 wherein:
R¹ is fluorine;
R² is hydrogen; and
10 R³ is methyl.

153. The compound of claim 137 wherein:
R¹ is methyl;
R² is hydrogen; and
15 R³ is methyl.

154. The compound of claim 137 wherein:
R¹ is hydrogen;
R² is methyl; and
20 R³ is methyl.

155. The compound of claim 137 wherein:
R¹ is methyl;
R² is methyl; and
25 R³ is methyl.

156. The compound of claim 136 wherein:
R¹ is selected from the group consisting of hydrogen, halo and C₁-C₅ alkyl,
said C₁-C₅ alkyl optionally substituted by alkoxy or one or more fluorine;

R^2 is selected from the group consisting of hydrogen, halo and C_1-C_5 alkyl, said C_1-C_5 alkyl optionally substituted by alkoxy or one or more fluorine; and
 R^3 is C_1-C_5 alkyl optionally substituted by alkoxy or one or more halo.

5

157. The compound of claim 156 wherein:

R^1 is selected from the group consisting of hydrogen and fluorine;
 R^2 is C_1-C_3 alkyl substituted by one or more halo; and
 R^3 is methyl.

10

158. The compound of claim 157 wherein:

R^1 is hydrogen;
 R^2 is CH_2F ; and
 R^3 is methyl.

15

159. The compound of claim 156 wherein:

R^1 is CH_2F ;
 R^2 is hydrogen; and
 R^3 is methyl.

20

160. The compound of claim 159 wherein:

R^1 is hydrogen;
 R^2 is hydrogen; and
 R^3 is CH_2F .

25

161. The compound of claim 159 wherein:

R^1 is hydrogen;
 R^2 is methoxymethyl; and
 R^3 is methyl.

30

162. The compound of claim 156 wherein:

R¹ is methoxymethyl;

R² is hydrogen; and

R³ is methyl.

5

163. The compound of claim 156 wherein:

R¹ is hydrogen;

R² is hydrogen; and

R³ is methoxymethyl.

10

164. The compound of claim 135 wherein the compound is the E isomer.

165. The compound of claim 164 wherein:

15

R¹ is selected from the group consisting of hydrogen, halo, and C₁-C₅ alkyl, said C₁-C₅ alkyl optionally substituted by halo or alkoxy, said alkoxy optionally substituted by one or more halo;

R² is selected from the group consisting of hydrogen, halo and C₁-C₅ alkyl, said C₁-C₅ alkyl optionally substituted by halo or alkoxy, said alkoxy optionally substituted by one or more halo; and

20

R³ is C₁-C₅ alkyl, said C₁-C₅ alkyl optionally substituted by one or more halo or alkoxy.

166. The compound of claim 165 wherein:

25

R¹ is selected from the group consisting of hydrogen, halo, and C₁-C₃ alkyl; said C₁-C₅ alkyl optionally substituted by halo or alkoxy, said alkoxy optionally substituted by one or more halo;

R² is selected from the group consisting of hydrogen, halo and C₁-C₅ alkyl; and

R³ is C₁-C₅ alkyl, said C₁-C₅ alkyl optionally substituted by halo or alkoxy

30

167. The compound of claim 165 wherein:

R^1 is selected from the group consisting of hydrogen, halo, and C_1 - C_3 alkyl;

R^2 is selected from the group consisting of hydrogen, halo and C_1 - C_3 alkyl;

and

5 R^3 is C_1 - C_3 alkyl optionally substituted by fluorine.

168. The compound of claim 165 wherein:

R^1 is selected from the group consisting of hydrogen, halo, and C_1 - C_3 alkyl;

R^2 is selected from the group consisting of hydrogen, halo and C_1 - C_3 alkyl;

10 and

R^3 is C_1 - C_5 alkyl, said C_1 - C_5 alkyl optionally substituted by fluorine or alkoxy.

169. The compound of claim 165 wherein:

15 R^1 is selected from the group consisting of hydrogen, halo, and C_1 - C_3 alkyl;

R^2 is selected from the group consisting of hydrogen, halo and C_1 - C_3 alkyl;

and

R^3 is C_1 - C_3 alkyl.

20 170. The compound of claim 165 wherein:

R^1 is hydrogen;

R^2 is selected from the group consisting of hydrogen, halo and C_1 - C_3 alkyl;

and

R^3 is C_1 - C_3 alkyl.

25

171. The compound of claim 170 wherein:

R^1 is hydrogen;

R^2 is selected from the group consisting of hydrogen and halo; and

R^3 is C_1 - C_3 alkyl.

30

172. The compound of claim 171 wherein:

R¹ is hydrogen;

R² is selected from the group consisting of hydrogen and fluorine; and

R³ is C₁-C₃ alkyl.

5

173. The compound of claim 172 wherein:

R¹ is hydrogen;

R² is selected from the group consisting of hydrogen and fluorine; and

R³ is methyl.

10

174. The compound of claim 172 wherein:

R¹ is hydrogen;

R² is hydrogen; and

R³ is methyl.

15

175. The compound of claim 173 wherein:

R¹ is hydrogen;

R² is fluorine; and

R³ is methyl.

20

176. The compound of claim 165 wherein:

R¹ is halo;

R² is selected from the group consisting of hydrogen, halo and C₁-C₃ alkyl;

and

25

R³ is C₁-C₃ alkyl.

177. The compound of claim 176 wherein:

R¹ is halo;

R² is halo; and

30

R³ is C₁-C₃ alkyl.

178. The compound of claim 177 wherein:

R¹ is fluorine;

R² is fluorine; and

5 R³ is methyl.

179. The compound of claim 176 wherein:

R¹ is fluorine;

R² is selected from the group consisting of hydrogen and C₁-C₃ alkyl; and

10 R³ is methyl.

180. The compound of claim 179 wherein:

R¹ is fluorine;

R² is hydrogen; and

15 R³ is methyl.

181. The compound of claim 165 wherein:

R¹ is methyl;

R² is hydrogen; and

20 R³ is methyl.

182. The compound of claim 165 wherein:

R¹ is hydrogen;

R² is methyl; and

25 R³ is methyl.

183. The compound of claim 165 wherein:

R¹ is methyl;

R² is methyl; and

30 R³ is methyl.

184. The compound of claim 164 wherein:

R¹ is selected from the group consisting of hydrogen, halo and C₁-C₅ alkyl,
said C₁-C₅ alkyl optionally substituted by alkoxy or one or more fluorine;

5 R² is selected from the group consisting of hydrogen, halo and C₁-C₅ alkyl,
said C₁-C₅ alkyl optionally substituted by alkoxy or one or more fluorine;

and

R³ is methyl optionally substituted by one or more alkoxy or halo.

185. The compound of claim 184 wherein:

10 R¹ is selected from the group consisting of hydrogen and fluorine;

R² is C₁-C₃ alkyl substituted by one or more halo; and

R³ is methyl.

186. The compound of claim 185 wherein:

15 R¹ is hydrogen;

R² is CH₂F; and

R³ is methyl.

187. The compound of claim 185 wherein:

20 R¹ is CH₂F;

R² is hydrogen; and

R³ is methyl.

188. The compound of claim 184 wherein:

25 R¹ is hydrogen;

R² is hydrogen; and

R³ is CH₂F.

189. The compound of claim 184 wherein:

30 R¹ is hydrogen;

R^2 is methoxymethyl; and

R^3 is methyl.

190. The compound of claim 184 wherein:

5 R^1 is methoxymethyl;

R^2 is hydrogen; and

R^3 is methyl.

191. The compound of claim 184 wherein:

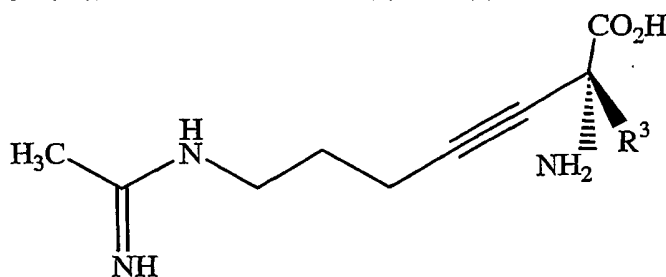
10 R^1 is hydrogen;

R^2 is hydrogen; and

R^3 is methoxymethyl.

192. A compound of Formula VI

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VI

or a pharmaceutically acceptable salt thereof, wherein:

20 R^3 is C_1 - C_5 alkyl, said C_1 - C_5 alkyl optionally substituted by halo or alkoxy,
said alkoxy optionally substituted by one or more halo.

193. The compound of claim 192 wherein:

R^3 is C_1 - C_5 alkyl substituted by one or more halo.

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194. The compound of claim 193 wherein:

R^3 is C_1 - C_5 alkyl substituted by one or more fluorine.

195. The compound of claim 193 wherein:

R^3 is methyl substituted by one or more halo.

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196. The compound of claim 195 wherein:

R^3 is methyl substituted by one or more fluorine.

197. The compound of claim 195 wherein:

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R^3 is CH_2F .

198. The compound recited in claim 193 wherein:

R^3 is C_1 - C_5 alkyl substituted by alkoxy.

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199. The compound of claim 198 wherein:

R^3 is methoxy methyl.

200. The compound of claim 193 wherein:

R^3 is C_1 - C_5 alkyl.

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201. The compound of claim 199 wherein:

R^3 is methyl.

202. A compound selected from the group consisting of:

25

(2*S*,3*Z*)-2-amino-2-methyl-4-fluoro-7-[(1-iminoethyl)amino]-3-heptenoic acid;

(2*S*,3*E*)-2-amino-2-methyl-4-fluoro-7-[(1-iminoethyl)amino]-3-heptenoic acid;

(3*Z*)-2-amino-2-methyl-3-fluoro-7-[(1-iminoethyl)amino]-3-heptenoic acid;

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(3*E*)-2-amino-2-methyl-3-fluoro-7-[(1-iminoethyl)amino]-3-heptenoic acid,
dihydrochloride;

- (3E)- 2-amino-2-methyl-3,4-difluoro-7-[(1-iminoethyl)amino]- 3-heptenoic acid;
- 5 (3Z)- 2-amino-2-methyl-3,4-difluoro-7-[(1-iminoethyl)amino]- 3-heptenoic acid;
- (2S,3E)-2-amino-2-methyl-7-[(1-iminoethyl)amino]-3-heptenoic acid;
- (2S,3Z)-2-amino-2-methyl-7-[(1-iminoethyl)amino]-3-heptenoic acid;
- 10 (2R,3E)-2-amino-2-methyl-7-[(1-iminoethyl)amino]-3-heptenoic acid;
- (2R,3Z)-2-amino-2-methyl-7-[(1-iminoethyl)amino]-3-heptenoic acid;
- 15 (3E)- 2-amino-2,3-dimethyl-7-[(1-iminoethyl)amino]-3-heptenoic acid;
- (3Z)-2-amino-2,3-dimethyl-7-[(1-iminoethyl)amino]-3-heptenoic acid;
- (3E)-2-amino-2,3,4-trimethyl-7-[(1-iminoethyl)amino]- 3-heptenoic acid;
- 20 (3Z)-2-amino-2,3,4-trimethyl-7-[(1-iminoethyl)amino]- 3-heptenoic acid;
- (3E)-2-amino-2,4-dimethyl-7-[(1-iminoethyl)amino]- 3-heptenoic acid;
- 25 (3Z)-2-amino-2,4-dimethyl-7-[(1-iminoethyl)amino]- 3-heptenoic acid;
- 2-amino-2-methyl-7-[(1-iminoethyl)amino]-3-heptynoic acid;
- (2S,3E)-2-amino-2-methyl-4-fluoro-7-[(1-iminoethyl)amino]-3-heptenoic acid, dihydrochloride;
- 30 (3Z)- 2-amino-2-methyl-3-fluoro-7-[(1-iminoethyl)amino]-3-heptenoic acid, dihydrochloride;
- 35 (3E)-2-amino-2-methyl-3-fluoro-7-[(1-iminoethyl)amino]-3-heptenoic acid, dihydrochloride;
- (3E)- 2-amino-2-methyl-3,4-difluoro-7-[(1-iminoethyl)amino]- 3-heptenoic acid, dihydrochloride;
- 40 (3Z)- 2-amino-2-methyl-3,4-difluoro-7-[(1-iminoethyl)amino]- 3-heptenoic acid, dihydrochloride;
- (2S,3E)-2-amino-2-methyl-7-[(1-iminoethyl)amino]-3-heptenoic acid, dihydrochloride;
- 45

- (2*S*,3*Z*)-2-amino-2-methyl-7-[(1-iminoethyl)amino]-3-heptenoic acid, dihydrochloride;
- 5 (2*R*,3*E*)-2-amino-2-methyl-7-[(1-iminoethyl)amino]-3-heptenoic acid, dihydrochloride;
- (2*R*,3*Z*)-2-amino-2-methyl-7-[(1-iminoethyl)amino]-3-heptenoic acid, dihydrochloride;
- 10 (3*E*)-2-amino-2,3-dimethyl-7-[(1-iminoethyl)amino]-3-heptenoic acid, dihydrochloride;
- (3*Z*)-2-amino-2,3-dimethyl-7-[(1-iminoethyl)amino]-3-heptenoic acid, dihydrochloride;
- 15 (3*E*)-2-amino-2,3,4-trimethyl-7-[(1-iminoethyl)amino]-3-heptenoic acid, dihydrochloride;
- (3*Z*)-2-amino-2,3,4-trimethyl-7-[(1-iminoethyl)amino]-3-heptenoic acid, dihydrochloride;
- 20 (3*E*)-2-amino-2,4-dimethyl-7-[(1-iminoethyl)amino]-3-heptenoic acid, dihydrochloride;
- 25 (3*Z*)-2-amino-2,4-dimethyl-7-[(1-iminoethyl)amino]-3-heptenoic acid, dihydrochloride; and
- 2-amino-2-methyl-7-[(1-iminoethyl)amino]-3-heptynoic acid, dihydrochloride.
- 30
203. A novel intermediate compound selected from the group consisting of:
- Methyl 2-methylserinate;
- 35 (3*Z*)-2-[(*tert*-butoxycarbonyl)amino]-6-cyano-2-methylhex-3-enoic acid;
- (3*Z*)-2-amino-6-cyano-2-methylhex-3-enoic acid;
- 40 (3*Z*)-2-amino-6-(ethanimidoylamino)-2-methylhex-3-enoic acid;
- Methyl 2-methylserinate hydrochloride;
- Methyl *N*-(*tert*-butoxycarbonyl)-2-methylserinate;
- 45

- Methyl 2-[(tert-butoxycarbonyl)amino]-2-methyl-3-oxopropanoate;
- Methyl (3Z)-2-[(tert-butoxycarbonyl)amino]-6-cyano-2-methylhex-3-enoate;
- 5 Methyl (3E)-2-[(tert-butoxycarbonyl)amino]-6-cyano-2-methylhex-3-enoate;
- Methyl (2S,3Z)-2-[(tert-butoxycarbonyl)amino]-6-cyano-2-methylhex-3-enoate;
- Methyl (2R,3Z)-2-[(tert-butoxycarbonyl)amino]-6-cyano-2-methylhex-3-enoate;
- 10 Methyl (2S,3E)-2-[(tert-butoxycarbonyl)amino]-6-cyano-2-methylhex-3-enoate;
- Methyl (2R,3E)-2-[(tert-butoxycarbonyl)amino]-6-cyano-2-methylhex-3-enoate;
- 15 (3Z)-2-[(tert-butoxycarbonyl)amino]-6-cyano-2-methylhex-3-enoic acid
potassium salt;
- (3Z)-2-amino-6-cyano-2-methylhex-3-enoic acid hydrochloride; and
- 20 (3Z)-2-amino-6-(ethanimidoylamino)-2-methylhex-3-enoic acid
dihydrochloride.

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(54) Title: 2-AMINO-2-ALKYL-3 HEPTENOIC AND HEPTYNOIC ACID DERIVATIVES USEFUL AS NITRIC OXIDE SYNTHASE INHIBITORS

(57) Abstract: The present invention relates to 2-amino-2-alkyl-3 heptenoic and heptynoic as derivatives and their use in therapy, in particular their use as nitric oxide synthase inhibitors.

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INTERNATIONAL SEARCH REPORT

International Application No

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A. CLASSIFICATION OF SUBJECT MATTER

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A61P19/02

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B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 99 46240 A (BERGMANIS ARIJA A ; SEARLE & CO (US); TOTH MIHALY V (US); AWASTHI A) 16 September 1999 (1999-09-16) page 4, line 16 -page 7, line 17 examples 7,8	1-202
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Patent family members are listed in annex.

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 01/28684

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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A	<p>LEE, Y ET AL : "Conformationally-restricted arginine analogues as alternative substrates and inhibitors of nitric oxide synthases" BIOORGANIC & MEDICINAL CHEMISTRY., vol. 7, 1999, pages 1097-1104, XP002197284 ELSEVIER SCIENCE LTD., GB ISSN: 0968-0896 cited in the application page 1098, paragraph 2 page 1099, line 8 - line 12 page 1101, "conclusion"</p>	1-202
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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II INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

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